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(54) Title: NOVEL MOLECULES OF THE TANGO-77 RELATED PROTEIN FAMILY AND USES THEREOF (57) Abstract Novel Tango-77 polypeptides, proteins, and nucleic acid molecules are disclosed. In addition to isolated, full-length Tango-77 proteins, the invention further provides isolated Tango-77 fusion proteins, antigenic peptides and anti-Tango-77 antibodies. The invention also provides Tango-77 nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a Tango-77 gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.		

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NOVEL MOLECULES OF THE TANGO-77 RELATED PROTEIN
FAMILY AND USES THEREOF

Background of the Invention

The polypeptide cytokine interleukin-1 (IL-1) is a critical mediator of inflammatory and overall immune response. To date, three members of the IL-1 family, IL-1 α , IL-1 β and IL-1ra (Interleukin-1 receptor antagonist) have been isolated and cloned. IL-1 α and IL-1 β are proinflammatory cytokines which elicit biological responses, whereas IL-1ra is an antagonist of IL-1 α and IL-1 β activity. Two distinct cell-surface receptors have been identified for these ligands, the type I IL-1 receptor (IL-1RtI) and type II IL-1 receptor (IL-1RtII). Recent results suggest that the IL-1RtI is the receptor responsible for transducing a signal and producing biological effects.

As mentioned above, IL-1 is a key mediator of the host inflammatory response. While inflammation is an important homeostatic mechanism, aberrant inflammation has the potential for inducing damage to the host. Elevated IL-1 levels are known to be associated with a number of diseases particularly autoimmune diseases and inflammatory disorders.

Since IL-1ra is a naturally occurring inhibitor of IL-1, IL-1ra can be used to limit the aberrant and potentially deleterious effects of IL-1. In experimental animals, pretreatment with IL-1ra has been shown to prevent death resulting from lipopolysaccharide-induced sepsis. The relative absence of IL-1ra has also been suggested to play a role in human inflammatory bowel disease.

Summary of the Invention

The present invention is based, at least in part, on the discovery of a gene encoding Tango-77, a secreted

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protein that is predicted to be a member of the cytokine superfamily. The Tango-77 cDNA described below (SEQ ID NO:1) has three possible open reading frames. The first potential open reading frame encompasses 534 nucleotides
5 extending from nucleotide 356 to nucleotide 889 of SEQ ID NO:1 (SEQ ID NO:3) and encodes a 178 amino acid protein (SEQ ID NO:2). This protein may include a predicted signal sequence of about 63 amino acids (from about amino acid 1 to about amino acid 63 of SEQ ID NO:2 (SEQ ID
10 NO:4) and a predicted mature protein of about 115 amino acids (from about amino acid 64 to amino acid 178 of SEQ ID NO:2 (SEQ ID NO:5)).

The second potential open reading frame encompasses 498 nucleotides extending from nucleotide 389
15 to nucleotide 889 of SEQ ID NO:1 (SEQ ID NO:6) and encodes a 167 amino acid protein (SEQ ID NO:7). This protein may include a predicted signal sequence of about 52 amino acids (from about amino acid 1 to about amino acid 52 of SEQ ID NO:7 (SEQ ID NO:8)) and a predicted
20 mature protein of about 115 amino acids (from about amino acid 52 to amino acid 167 of SEQ ID NO:7 (SEQ ID NO:9)).

The third potential open reading frame encompasses 408 nucleotides extending from nucleotide 481 to nucleotide 889 of SEQ ID NO:1 (SEQ ID NO:10) and encodes
25 a 136 amino acid protein (SEQ ID NO:11). This protein includes a predicted signal sequence of about 21 amino acids (from about amino acid 1 to about amino acid 21 of SEQ ID NO:11 (SEQ ID NO:12)) and a predicted mature protein of about 115 amino acids (from about amino acid
30 22 to amino acid 136 of SEQ ID NO:11 (SEQ ID NO:13)).

As used herein, the terms "Tango-77", "Tango-77 protein", "Tango-77 polypeptide" and the like, can refer and polypeptide produced by the cDNA of SEQ ID NO:1 including any and all of the Tango-77 gene products
35 described above.

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Tango-77 is expected to inhibit inflammation and play a functional role similar to that of secreted IL-1ra. For example, it is expected that Tango-77 may bind to the IL-1 receptor, thus blocking receptor
5 activation by inhibiting the binding of IL-1 α and IL-1 β to the receptor. Alternatively, Tango-77 may inhibit inflammation through another pathway, for example, by binding to a novel receptor. Accordingly, Tango-77 may be useful as a modulating agent in regulating a variety
10 of cellular processes including acute and chronic inflammation, e.g., asthma, chronic myelogenous leukemia, rheumatoid arthritis, psoriasis and inflammatory bowel disease.

In one aspect, the invention provides isolated
15 nucleic acid molecules encoding Tango-77 or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection of Tango-77.

The invention encompasses methods of diagnosing
20 and treating patients who are suffering from a disorder associated with an abnormal level (undesirably high or undesirably low) of inflammation, abnormal activity of the IL-1 receptor complex, or abnormal activity of IL-1, by administering a compound that modulates the expression
25 of Tango-77 (at the DNA, mRNA or protein level, e.g., by altering mRNA splicing) or by altering the activity of Tango-77. Examples of such compounds include small molecules, antisense nucleic acid molecules, ribozymes, and polypeptides.

30 The invention features a nucleic acid molecule which is at least 45% (e.g., 55%, 65%, 75%, 85%, 95%, or 98%) identical to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the nucleotide sequence of the cDNA insert of the plasmid

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deposited with ATCC as Accession Number (the "cDNA of ATCC 98807"), or a complement thereof.

The invention features a nucleic acid molecule which includes a fragment of at least 100 (e.g., 250, 325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, or 989) nucleotides of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the nucleotide sequence of the cDNA ATCC 98807, or a complement thereof.

10 The invention also features a nucleic acid molecule which includes a nucleotide sequence encoding a protein having an amino acid sequence that is at least 45% (55%, 65%, 75%, 85%, 95%, or 98%) identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, or the amino acid sequence encoded by the cDNA of ATCC 98807.

In a preferred embodiment, a Tango-77 nucleic acid molecule has the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or the nucleotide sequence of the cDNA of ATCC 98807.

Also within the invention is a nucleic acid molecule which encodes a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, wherein the fragment includes at least 15 (e.g., 25, 30, 50, 100, 150, or 178) contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or the polypeptide encoded by the cDNA of ATCC Accession Number 98807.

The invention includes a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or

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an amino acid sequence encoded by the cDNA of ATCC Accession Number 98807, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or a
5 complement thereof under stringent conditions.

Also within the invention are: an isolated Tango-77 protein having an amino acid sequence that is at least about 45%, preferably 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:5, SEQ
10 ID NO:9 or SEQ ID NO:13 (mature human Tango-77), or the amino acid sequence of SEQ ID NO:2, SEQ ID NO:7 or SEQ ID NO:11 (immature human Tango-77).

Also within the invention are: an isolated Tango-77 protein which is encoded by a nucleic acid
15 molecule having a nucleotide sequence that is at least about 65%, preferably 75%, 85%, or 95% identical to SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or the cDNA of ATCC 98807; and an isolated Tango-77 protein which is encoded by a nucleic acid molecule having a nucleotide sequence
20 which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the non-coding strand of the cDNA of ATCC 98807, or the complement thereof.

25 Also within the invention is a polypeptide which is a naturally occurring allelic variant of a polypeptide that includes the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an
30 amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID

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NO:10 or the complement thereof under stringent conditions.

Another embodiment of the invention features Tango-77 nucleic acid molecules which specifically detect
5 Tango-77 nucleic acid molecules relative to nucleic acid molecules encoding other members of the cytokine superfamily. For example, in one embodiment, a Tango-77 nucleic acid molecule hybridizes under stringent conditions to a nucleic acid molecule comprising the
10 nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA of ATCC 98807, or a complement thereof. In another embodiment, the Tango-77 nucleic acid molecule is at least 300 (325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, or 989)
15 nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA of ATCC 98807, or a complement thereof. In yet another embodiment, the
20 invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a Tango-77 nucleic acid.

Another aspect of the invention provides a vector, e.g., a recombinant expression vector, comprising a
25 Tango-77 nucleic acid molecule of the invention. In another embodiment, the invention provides a host cell containing such a vector. The invention also provides a method for producing Tango-77 protein by culturing, in a suitable medium, a host cell of the invention containing
30 a recombinant expression vector such that a Tango-77 protein is produced.

Another aspect of this invention features isolated or recombinant Tango-77 proteins and polypeptides. Preferred Tango-77 proteins and polypeptides possess at
35 least one biological activity possessed by naturally

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occurring human Tango-77, e.g., (i) the ability to interact with proteins in the Tango-77 signalling pathway (ii) the ability to interact with a Tango-77 ligand or receptor; or (iii) the ability to interact with an intracellular target protein, (iv) the ability to interact with a protein involved in inflammation and (v) the ability to bind the IL-1 receptor. Other activities include the induction and suppression of polypeptide interleukins, cytokines and growth factors.

10 The Tango-77 proteins of the present invention, or biologically active portions thereof, can be operably linked to a non-Tango-77 polypeptide (e.g., heterologous amino acid sequences) to form Tango-77 fusion proteins. The invention further features antibodies that specifically bind Tango-77 proteins, such as monoclonal or polyclonal antibodies. In addition, the Tango-77 proteins or biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

20 In another aspect, the present invention provides a method for detecting the presence of Tango-77 activity or expression in a biological sample by contacting the biological sample with an agent capable of detecting an indicator of Tango-77 activity or expression such that the presence of Tango-77 activity or expression is detected in the biological sample.

 In another aspect, the invention provides a method for modulating Tango-77 activity comprising contacting a cell with an agent that modulates (inhibits or stimulates)

30 Tango-77 activity or expression such that Tango-77 activity or expression in the cell is modulated. In one embodiment, the agent is an antibody that specifically binds to Tango-77 protein. In another embodiment, the

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agent modulates expression of Tango-77 by modulating transcription of a Tango-77 gene, splicing of a Tango-77 mRNA, or translation of a Tango-77 mRNA. In yet another embodiment, the agent is a nucleic acid molecule having a
5 nucleotide sequence that is antisense to the coding strand of the Tango-77 mRNA or the Tango-77 gene.

In one embodiment, the methods of the present invention are used to treat a subject having a disorder characterized by aberrant Tango-77 protein activity or
10 nucleic acid expression by administering an agent which is a Tango-77 modulator to the subject. In one embodiment, the Tango-77 modulator is a Tango-77 protein. In another embodiment, the Tango-77 modulator is a Tango-77 nucleic acid molecule. In other embodiments,
15 the Tango-77 modulator is a peptide, peptidomimetic, or other small molecule. In a preferred embodiment, the disorder characterized by aberrant Tango-77 protein or nucleic acid expression can include chronic and acute inflammation.

20 The present invention also provides a diagnostic assay for identifying the presence or absence of a genetic lesion or mutation characterized by at least one of: (i) aberrant modification or mutation of a gene encoding a Tango-77 protein; (ii) mis-regulation of a
25 gene encoding a Tango-77 protein; and (iii) aberrant post-translational modification of a Tango-77 protein, wherein a wild-type form of the gene encodes a protein with a Tango-77 activity.

In another aspect, the invention provides a
30 method for identifying a compound that binds to or modulates the activity of a Tango-77 protein. In general, such methods entail measuring a biological activity of a Tango-77 protein in the presence and absence of a test compound and identifying those

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compounds which alter the activity of the Tango-77 protein.

The invention also features methods for identifying a compound which modulates the expression of Tango-77 by measuring the expression of Tango-77 in the presence and absence of a compound.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

10 Brief Description of the Drawings

Figure 1 depicts the cDNA sequence (SEQ ID NO:1) of Tango-77. The Tango-77 cDNA has three possible open reading frames which encode the amino acid sequence (SEQ ID NO:2, SEQ ID NO:7 and SEQ ID NO:11) of human Tango-77. The three potential open reading frames of SEQ ID NO:1 extend from: (1) nucleotide 356 to nucleotide 889 (SEQ ID NO:3); (2) nucleotide 389 to nucleotide 889 (SEQ ID NO:6); and (3) nucleotide 481 to nucleotide 889 (SEQ ID NO:10).

20 Figure 2 depicts an alignment of an amino acid sequence of Tango-77 (T77; SEQ ID NO:2) with IL-1RA (SEQ ID NO:14), and IL-1 β (SEQ ID NO:15).

Figure 3 depicts the genomic sequence of BAC1 (SEQ ID NO:16).

25 Figure 4 depicts the genomic sequence of BAC2 (SEQ ID NO:17).

Figure 5 depicts an amino acid sequence of an alternatively spliced form of Tango-77 (SEQ ID NO:2) as predicted by Procrustes (T77-procrustes; SEQ ID NO:18).

30 Figure 6 depicts an alignment of an amino acid sequence of an alternatively spliced form of Tango-77 (T77-procrustes; SEQ ID NO:18) with Tango-77 (SEQ ID NO:2).

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Figure 7 depicts an alignment of an amino acid sequence of an alternatively spliced form of Tango-77 (T77-procrustes; SEQ ID NO:18) with IL-1ra (SEQ ID NO:14), and IL-1 β (SEQ ID NO:15).

5 Detailed Description of the Invention

The present invention is based on the discovery of a cDNA molecule encoding human Tango-77, a member of the cytokine superfamily. The cDNA molecule encoding human Tango-77 has three possible open reading frames. The
10 three possible nucleotide open reading frames for human Tango-77 protein are shown in Figure 1 (SEQ ID NO:3, SEQ ID NO:6 and SEQ ID NO:10). The predicted amino acid sequence for the three possible Tango-77 immature proteins are also shown in
15 Figure 1 (SEQ ID NO:2, SEQ ID NO:7 or SEQ ID NO:11) and three possible mature proteins are also shown in Figure 1 (SEQ ID NO:5, SEQ ID NO:9 and SEQ ID NO:13).

The Tango-77 cDNA of Figure 1 (SEQ ID NO:1), which is approximately 989 nucleotides long including
20 untranslated regions, encodes a protein amino acid having a molecular weight of approximately 19 kDa, 18 kDa, or 14.9 kDa (excluding post-translational modifications) and the possible mature form of the protein has a molecular weight of 13 kDa. A plasmid containing a cDNA encoding
25 human Tango-77 (with the cDNA insert name of Of fthx077) was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 on July 2, 1998 and assigned Accession Number 98807. This deposit will be maintained under the terms
30 of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an

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admission that a deposit is required under 35 U.S.C. §112.

Human Tango-77 is one member of a family of molecules (the "Tango-77 family") having certain
5 conserved structural and functional features. The term "family," when referring to the protein and nucleic acid molecules of the invention, is intended to mean two or more proteins or nucleic acid molecules having a common structural domain and having sufficient amino acid or
10 nucleotide sequence identity as defined herein. Such family members can be naturally occurring and can be from either the same or different species. For example, a family can contain a first protein of human origin and a homologue of that protein of murine origin, as well as a
15 second, distinct protein of human origin and a murine homologue of that protein. Members of a family may also have common functional characteristics.

As used interchangeably herein a "Tango-77 activity", "biological activity of Tango-77" or
20 "functional activity of Tango-77", refers to an activity exerted by a Tango-77 protein, polypeptide or nucleic acid molecule on a Tango-77 responsive cell as determined *in vivo*, or *in vitro*, according to standard techniques. A Tango-77 activity can be a direct activity, such as an
25 association with a second protein, or an indirect activity, such as a cellular signaling activity mediated by interaction of the Tango-77 protein with a second protein. In a preferred embodiment, a Tango-77 activity includes at least one or more of the following
30 activities: (i) the ability to interact with proteins in the Tango-77 signalling pathway (ii) the ability to interact with a Tango-77 ligand or receptor; or (iii) the ability to interact with an intracellular target protein, (iv) the ability to interact with a protein involved in

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inflammation, and (v) the ability to bind the IL-1 receptor.

Accordingly, another embodiment of the invention features isolated Tango-77 proteins and polypeptides
5 having a Tango-77 activity.

Yet another embodiment of the invention features Tango-77 molecules which contain a signal sequence. Generally, a signal sequence (or signal peptide) is a peptide containing about 21 to 63 amino acids which
10 occurs at the extreme N-terminal end of a secretory protein. The native Tango-77 signal sequence (SEQ ID NO:4, SEQ ID NO:8, or SEQ ID NO:12) can be removed and replaced with a signal sequence from another protein. In certain host cells (e.g., mammalian host cells),
15 expression and/or secretion of Tango-77 can be increased through use of a heterologous signal sequence. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence. Alternatively, the native Tango-77 signal
20 sequence can itself be used as a heterologous signal sequence in expression systems, e.g., to facilitate the secretion of a protein of interest.

Various aspects of the invention are described in further detail in the following subsections.

25 I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode Tango-77 proteins or biologically active portions thereof, as well as nucleic acid molecules sufficient for use as hybridization probes
30 to identify Tango-77-encoding nucleic acids (e.g., Tango-77 mRNA) and fragments for use as PCR primers for the amplification or mutation of Tango-77 nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g.,

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cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences (preferably protein encoding sequences) which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated Tango-77 nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA of ATCC 98807, or a complement of any of these nucleotide sequences, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA of ATCC 98807, or the complement thereof as a hybridization probe, Tango-77 nucleic acid molecules can be isolated using standard

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hybridization and cloning techniques (e.g., as described in Sambrook et al., eds., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid of the invention can be amplified using cDNA, mRNA or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to Tango-77 nucleotide sequences can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 the cDNA of ATCC 98807, or a portion thereof. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding Tango-77, for example, a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of Tango-77. The nucleotide sequence determined from the cloning of the human Tango-77 gene allows for the generation of probes and primers designed for use in identifying and/or cloning Tango-77 homologues in other cell types, e.g., from other tissues, as well as Tango-77 homologues from other mammals. The probe/primer typically comprises

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substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive nucleotides of the sense or anti-sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807. Alternatively, the oligonucleotide can typically comprise a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive nucleotides of the sense or anti-sense sequence of a naturally occurring mutant of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807.

Probes based on the human Tango-77 nucleotide sequence can be used to detect transcripts or genomic sequences encoding the same or identical proteins. The probe comprises a label group attached thereto, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express a Tango-77 protein, such as by measuring a level of a Tango-77-encoding nucleic acid in a sample of cells from a subject, e.g., detecting Tango-77 mRNA levels or determining whether a genomic Tango-77 gene has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion of Tango-77" can be prepared by isolating a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or the nucleotide sequence of the cDNA of ATCC 98807 which encodes a polypeptide having a Tango-77 biological activity, expressing the encoded portion of Tango-77 protein (e.g., by recombinant expression in

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vitro) and assessing the activity of the encoded portion of Tango-77.

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807 due to degeneracy of the genetic code and thus encode the same Tango-77 protein as that encoded by the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807.

In addition to the human Tango-77 nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of Tango-77 may exist within a population (e.g., the human population). Such genetic polymorphism in the Tango-77 gene may exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. As used herein, the term "allelic variant" refers to a nucleotide sequence which occurs at a Tango-77 locus or to a polypeptide encoded by the nucleotide sequence. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a Tango-77 protein, preferably a mammalian Tango-77 protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the Tango-77 gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations in

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Tango-77 that are the result of natural allelic variation and that do not alter the functional activity of Tango-77 are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding Tango-77
5 proteins from other species (Tango-77 homologues), which have a nucleotide sequence which differs from that of a human Tango-77, are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the Tango-77
10 cDNA of the invention can be isolated based on their identity to the human Tango-77 nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

15 Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 300 (325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, or 989) nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule
20 comprising the nucleotide sequence, preferably the coding sequence, of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions
25 for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in Current Protocols
30 in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at
35 50-65°C. Preferably, an isolated nucleic acid molecule

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of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA of ATCC 98807, or the complement thereof, corresponds to a naturally-occurring
5 nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

In addition to naturally-occurring allelic
10 variants of the Tango-77 sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or the cDNA of ATCC 98807, thereby
15 leading to changes in the amino acid sequence of the encoded Tango-77 protein, without altering the biological activity of the Tango-77 protein. Amino acid residues that are not conserved or only semiconserved among Tango-77 of various species may be non-essential for activity
20 and thus would likely be targets for alteration.

Alternatively, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-
25 type sequence of Tango-77 (e.g., the sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11 or SEQ ID NO:13) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino
30 acid residues that are conserved among the Tango-77 proteins of various species may be essential for activity and thus would not likely be targets for alteration, unless one wishes to reduce or alter Tango-77 activity.

Accordingly, another aspect of the invention
35 pertains to nucleic acid molecules encoding Tango-77

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proteins that contain changes in amino acid residues that are not essential for activity. Such Tango-77 proteins differ in amino acid sequence from SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a protein that includes an amino acid sequence that is at least about 45% identical, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13.

An isolated nucleic acid molecule encoding a Tango-77 protein having a sequence which differs from that of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the cDNA of ATCC 98807 such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine,

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valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

5 Thus, a predicted nonessential amino acid residue in Tango-77 is preferably replaced with another amino acid residue from the same side chain family. Alternatively, mutations can be introduced randomly along all or part of a Tango-77 coding sequence, such as by saturation
10 mutagenesis, and the resultant mutants can be screened for Tango-77 biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

15 In a preferred embodiment, a mutant Tango-77 protein can be assayed for: (1) the ability to form protein:protein interactions with proteins in the Tango-77 signalling pathway; (2) the ability to bind a Tango-77 ligand or receptor; or (3) the ability to bind
20 to an intracellular target protein or (4) the ability to interact with a protein involved in inflammation or (5) the ability to bind the IL-1 receptor. In yet another preferred embodiment, a mutant Tango-77 can be assayed for the ability to modulate inflammation, asthma,
25 autoimmune diseases, and sepsis.

The present invention encompasses antisense nucleic acid molecules, i.e., molecules which are complementary to a sense nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-
30 stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire Tango-77 coding strand, or to only a portion thereof, e.g., all or
35 part of the protein coding region (or open reading

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frame). An antisense nucleic acid molecule can be antisense to a noncoding region of the coding strand of a nucleotide sequence encoding Tango-77. The noncoding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

Given the coding strand sequences encoding Tango-77 disclosed herein (e.g., SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:8), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of Tango-77 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of Tango-77 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of Tango-77 mRNA, e.g., an oligonucleotide having the sequence 5'-TGCAACTTTTACAGGAAACAC-3' (SEQ ID NO:19) or 5'-CCTCACTTTTACCCGAGACTC-3' (SEQ ID NO:20) or 5'-GACGGGTGGTACTTAAACAA-3' (SEQ ID NO:21). An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to

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generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a Tango-77 protein to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which

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binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier et al. (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue et al. (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al. (1987) *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead

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ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave Tango-77 mRNA transcripts to thereby inhibit translation of Tango-77 mRNA. A ribozyme having specificity for a
5 Tango-77-encoding nucleic acid can be designed based upon the nucleotide sequence of a Tango-77 cDNA disclosed herein (e.g., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide
10 sequence of the active site is complementary to the nucleotide sequence to be cleaved in a Tango-77-encoding mRNA. See, e.g., Cech et al. U.S. Patent No. 4,987,071; and Cech et al. U.S. Patent No. 5,116,742. Alternatively, Tango-77 mRNA can be used to select a
15 catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel and Szostak (1993) *Science* 261:1411-1418.

The invention also encompasses nucleic acid molecules which form triple helical structures. For
20 example, Tango-77 gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the Tango-77 (e.g., the Tango-77 promoter and/or enhancers) to form triple helical structures that prevent transcription of the Tango-77
25 gene in target cells. See generally, Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

In preferred embodiments, the nucleic acid
30 molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate
35 peptide nucleic acids (see Hyrup et al. (1996) *Bioorganic*

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& *Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996) *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675.

PNAs of Tango-77 can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs of Tango-77 can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup (1996) *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup (1996) *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675).

In another embodiment, PNAs of Tango-77 can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of Tango-77 can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion

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would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation
5 (Hyrup (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996) *supra* and Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry
10 and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al. (1989) *Nucleic Acid Res.* 17:5973-88). PNA monomers are then coupled in a stepwise manner to
15 produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al. (1975) *Bioorganic Med. Chem. Lett.*
20 5:1119-11124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see,
25 e.g., Letsinger et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W0 88/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W0 89/10134). In addition, oligonucleotides can be
30 modified with hybridization-triggered cleavage agents (see, e.g., Krol et al. (1988) *Bio/Techniques* 6:958-976) or intercalating agents (see, e.g., Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide,

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hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

II. Isolated Tango-77 Proteins and Anti-Tango-77 Antibodies

5 One aspect of the invention pertains to isolated Tango-77 proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti-Tango-77 antibodies. In one embodiment, native Tango-77 proteins can be isolated
10 from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, Tango-77 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a Tango-77 protein or polypeptide
15 can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from
20 the cell or tissue source from which the Tango-77 protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of Tango-77 protein in which the
25 protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, Tango-77 protein that is substantially free of cellular material includes preparations of Tango-77 protein having less than about 30%, 20%, 10%, or
30 5% (by dry weight) of non-Tango-77 protein (also referred to herein as a "contaminating protein"). When the Tango-77 protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture

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medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When Tango-77 protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of Tango-77 protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or non-Tango-77 chemicals.

10 Biologically active portions of a Tango-77 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the Tango-77 protein (e.g., the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, 15 SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13), which include fewer amino acids than the full length Tango-77 proteins, and exhibit at least one activity of a Tango-77 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of 20 the Tango-77 protein. A biologically active portion of a Tango-77 protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length.

Moreover, other biologically active portions, in which other regions of the protein are deleted, can be 25 prepared by recombinant techniques and evaluated for one or more of the functional activities of a native Tango-77 protein.

Preferred Tango-77 protein has the amino acid sequence shown of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, 30 SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13. Other useful Tango-77 proteins are substantially identical to SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 and retain the functional activity of the protein of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, 35 SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 yet differ in

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amino acid sequence due to natural allelic variation or mutagenesis. Accordingly, a useful Tango-77 protein is a protein which includes an amino acid sequence at least about 45%, preferably 55%, 65%, 75%, 85%, 95%, or 99% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13 and retains the functional activity of the Tango-77 proteins of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13. In a preferred embodiment, the Tango-77 protein retains a functional activity of the Tango-77 protein of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or SEQ ID NO:13.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions, e.g., overlapping x 100). Preferably, the two sequences are the same length.

The determination of percent homology between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990)

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Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to Tango-77 nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to Tango-77 protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides Tango-77 chimeric or fusion proteins. As used herein, a Tango-77 "chimeric protein" or "fusion protein" comprises a Tango-77 polypeptide operably linked to a non-Tango-77 polypeptide. A "Tango-77 polypeptide" refers to a

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polypeptide having an amino acid sequence corresponding to Tango-77 polypeptides, whereas a "non-Tango-77 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially identical to the Tango-77 protein, e.g., a protein which is different from the Tango-77 protein and which is derived from the same or a different organism. Within a Tango-77 fusion protein the Tango-77 polypeptide can correspond to all or a portion of a Tango-77 protein, preferably at least one biologically active portion of a Tango-77 protein. Within the fusion protein, the term "operably linked" is intended to indicate that the Tango-77 polypeptide and the non-Tango-77 polypeptide are fused in-frame to each other. The non-Tango-77 polypeptide can be fused to the N-terminus or C-terminus of the Tango-77 polypeptide.

One useful fusion protein is a GST-Tango-77 fusion protein in which the Tango-77 sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant Tango-77.

In another embodiment, the fusion protein is a Tango-77 protein containing a heterologous signal sequence at its N-terminus. For example, the native Tango-77 signal sequence (i.e., about amino acids 1 to 63 of SEQ ID NO:2; SEQ ID NO:4; or about amino acids 1 to 52 of SEQ ID NO:7; SEQ ID NO:8; or about amino acids 1 to 21 of SEQ ID NO:11; SEQ ID NO:12) can be removed and replaced with a signal sequence from another protein. In certain host cells (e.g., mammalian host cells), expression and/or secretion of Tango-77 can be increased through use of a heterologous signal sequence. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel et al., *supra*). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of

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melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al.,
5 supra) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an Tango-77-immunoglobulin fusion protein in which all or part of Tango-77 is fused to sequences derived from a
10 member of the immunoglobulin protein family. The Tango-77-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a Tango-77 ligand and a Tango-77 receptor on the
15 surface of a cell, to thereby suppress Tango-77-mediated signal transduction *in vivo*. The Tango-77-immunoglobulin fusion proteins can be used to affect the bioavailability of a Tango-77 cognate ligand. Inhibition of the Tango-77 ligand/Tango-77 interaction may be useful therapeutically
20 for both the treatment of inflammatory and autoimmune disorders. Moreover, the Tango-77-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-Tango-77 antibodies in a subject, to purify Tango-77 ligands and in screening assays to identify
25 molecules which inhibit the interaction of Tango-77 with a Tango-77 receptor.

Preferably, a Tango-77 chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the
30 different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as
35 appropriate, alkaline phosphatase treatment to avoid

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undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, e.g., *Current Protocols in Molecular Biology*, Ausubel et al. eds., John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). An Tango-77-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the Tango-77 protein.

The present invention also pertains to variants of the Tango-77 proteins (i.e., proteins having a sequence which differs from that of the Tango-77 amino acid sequence). Such variants can function as either Tango-77 agonists (mimetics) or as Tango-77 antagonists. Variants of the Tango-77 protein can be generated by mutagenesis, e.g., discrete point mutation or truncation of the Tango-77 protein. An agonist of the Tango-77 protein can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the Tango-77 protein. An antagonist of the Tango-77 protein can inhibit one or more of the activities of the naturally occurring form of the Tango-77 protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the Tango-77 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer

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side effects in a subject relative to treatment with the naturally occurring form of the Tango-77 proteins.

Variants of the Tango-77 protein which function as either Tango-77 agonists (mimetics) or as Tango-77 antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the Tango-77 protein for Tango-77 protein agonist or antagonist activity. In one embodiment, a variegated library of Tango-77 variants is generated by
10 combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of Tango-77 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a
15 degenerate set of potential Tango-77 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display) containing the set of Tango-77 sequences therein. There are a variety of methods which can be
20 used to produce libraries of potential Tango-77 variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use
25 of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential Tango-77 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang (1983) *Tetrahedron* 39:3; Itakura et al. (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al. (1984) *Science* 198:1056; Ike et al. (1983) *Nucleic Acid Res.* 11:477).

In addition, libraries of fragments of the Tango-77 protein coding sequence can be used to generate
35 a variegated population of Tango-77 fragments for

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screening and subsequent selection of variants of a Tango-77 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a Tango-77 coding sequence with
5 a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed
10 duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal and internal fragments of various sizes of the Tango-77 protein.

15 Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the
20 gene libraries generated by the combinatorial mutagenesis of Tango-77 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors,
25 transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble
30 mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify Tango-77 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave et al. (1993)
35 *Protein Engineering* 6(3):327-331).

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An isolated Tango-77 protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind Tango-77 using standard techniques for polyclonal and monoclonal antibody preparation. The
5 full-length Tango-77 protein can be used or, alternatively, the invention provides antigenic peptide fragments of Tango-77 for use as immunogens. The antigenic peptide of Tango-77 comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues of the
10 amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11 or SEQ ID NO:13 and encompasses an epitope of Tango-77 such that an antibody raised against the peptide forms a specific immune complex with Tango-77.

15 A Tango-77 immunogen typically is used to prepare antibodies by immunizing a suitable subject (e.g., rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed Tango-77 protein or a
20 chemically synthesized Tango-77 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic Tango-77 preparation induces
25 a polyclonal anti-Tango-77 antibody response.

Accordingly, another aspect of the invention pertains to anti-Tango-77 antibodies. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of
30 immunoglobulin molecules, i.e., molecules that contain an antigen binding site which specifically binds an antigen, such as Tango-77. A molecule which specifically binds to Tango-77 is a molecule which binds Tango-77, but does not substantially bind other molecules in a sample, e.g., a
35 biological sample, which naturally contains Tango-77.

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Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides
5 polyclonal and monoclonal antibodies that bind Tango-77. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a
10 particular epitope of Tango-77. A monoclonal antibody composition thus typically displays a single binding affinity for a particular Tango-77 protein with which it immunoreacts.

Polyclonal anti-Tango-77 antibodies can be
15 prepared as described above by immunizing a suitable subject with a Tango-77 immunogen. The anti-Tango-77 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized
20 Tango-77. If desired, the antibody molecules directed against Tango-77 can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after
25 immunization, e.g., when the anti-Tango-77 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein
30 (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for
35 producing hybridomas is well known (see generally Current

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Protocols in Immunology (1994) Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a Tango-77 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds Tango-77.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-Tango-77 monoclonal antibody (see, e.g., Current Protocols in Immunology, supra; Galfre et al. (1977) *Nature* 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner (1981) *Yale J. Biol. Med.*, 54:387-402. Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (e.g., a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line, e.g., a myeloma cell line that is sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, e.g., the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused

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myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants
5 for antibodies that bind Tango-77, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-Tango-77 antibody can be identified and isolated by screening a recombinant
10 combinatorial immunoglobulin library (e.g., an antibody phage display library) with Tango-77 to thereby isolate immunoglobulin library members that bind Tango-77. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant
15 *Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example,
20 U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO
25 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J* 12:725-734.

Additionally, recombinant anti-Tango-77
30 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be
35 produced by recombinant DNA techniques known in the art,

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for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; 5 U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura 10 et al. (1987) *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al. (1986) *Nature* 15 321:552-525; Verhoeyan et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced using transgenic mice 20 which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of Tango-77. 25 Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic 30 mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion 35 of this technology for producing human antibodies and

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human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition,
5 companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to the described above.

Completely human antibodies which recognize a
10 selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope.

15 First, a non-human monoclonal antibody which binds a selected antigen (epitope), e.g., an antibody which inhibits Tango-77 activity, is identified. The heavy chain and the light chain of the non-human antibody are cloned and used to create phage display Fab fragments.
20 For example, the heavy chain gene can be cloned into a plasmid vector so that the heavy chain can be secreted from bacteria. The light chain gene can be cloned into a phage coat protein gene so that the light chain can be expressed on the surface of phage. A repertoire (random
25 collection) of human light chains fused to phage is used to infect the bacteria which express the non-human heavy chain. The resulting progeny phage display hybrid antibodies (human light chain/non-human heavy chain). The selected antigen is used in a panning screen to
30 select phage which bind the selected antigen. Several rounds of selection may be required to identify such phage. Next, human light chain genes are isolated from the selected phage which bind the selected antigen. These selected human light chain genes are then used to
35 guide the selection of human heavy chain genes as

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follows. The selected human light chain genes are inserted into vectors for expression by bacteria. Bacteria expressing the selected human light chains are infected with a repertoire of human heavy chains fused to
5 phage. The resulting progeny phage display human antibodies (human light chain/human heavy chain).

Next, the selected antigen is used in a panning screen to select phage which bind the selected antigen. The phage selected in this step display completely human
10 antibody which recognize the same epitope recognized by the original selected, non-human monoclonal antibody. The genes encoding both the heavy and light chains are readily isolated and be further manipulated for production of human antibody. This technology is
15 described by Jespers et al. (1994, *Bio/technology* 12:899-903).

An anti-Tango-77 antibody (e.g., monoclonal antibody) can be used to isolate Tango-77 by standard techniques, such as affinity chromatography or
20 immunoprecipitation. An anti-Tango-77 antibody can facilitate the purification of natural Tango-77 from cells and of recombinantly produced Tango-77 expressed in host cells. Moreover, an anti-Tango-77 antibody can be used to detect Tango-77 protein (e.g., in a cellular
25 lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the Tango-77 protein. Anti-Tango-77 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for
30 example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials,
35 bioluminescent materials, and radioactive materials.

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Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and
5 avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of
10 bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to
15 vectors, preferably expression vectors, containing a nucleic acid molecule encoding Tango-77 (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of
20 vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous
25 replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon
30 introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant

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DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression

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vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (e.g., Tango-77 proteins, mutant forms
5 of Tango-77, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of Tango-77 in prokaryotic or eukaryotic cells, e.g., bacterial cells such as *E. coli*, insect cells (using baculovirus
10 expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and
15 translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the
20 expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant
25 protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction
30 of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.
35 Typical fusion expression vectors include pGEX (Pharmacia

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Biotech Inc; Smith and Johnson (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein
5 A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al. (1988) *Gene* 69:301-315) and pET 11d (Studier et al., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press,
10 San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion
15 promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident λ prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

20 One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, *Gene Expression Technology: Methods in Enzymology* 185,
25 Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al.
30 (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the Tango-77 expression vector is a yeast expression vector. Examples of vectors
35 for expression in yeast *S. cerevisiae* include pYepSec1

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(Baldari et al. (1987) *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz (1982) *Cell* 30:933-943), pJRY88 (Schultz et al. (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and picZ (Invitrogen Corp,
5 San Diego, CA).

Alternatively, Tango-77 can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series
10 (Smith et al. (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a
15 mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed (1987) *Nature* 329:840) and pMT2PC (Kaufman et al. (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral
20 regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook et al. (*supra*).

25 In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory
30 elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al. (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular
35 promoters of T cell receptors (Winoto and Baltimore

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(1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji et al. (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund et al. (1985) *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to Tango-77 mRNA. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see

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Weintraub et al. (*Reviews - Trends in Genetics*, Vol. 1(1) 1986).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, Tango-77 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome.

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In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable
5 markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding Tango-77 or can be introduced on a separate vector. Cells stably
10 transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a
15 prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) Tango-77 protein. Accordingly, the invention further provides methods for producing Tango-77 protein using the host cells of the invention. In one embodiment, the method comprises
20 culturing the host cell of invention (into which a recombinant expression vector encoding Tango-77 has been introduced) in a suitable medium such that Tango-77 protein is produced. In another embodiment, the method further comprises isolating Tango-77 from the medium or
25 the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which
30 Tango-77-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous Tango-77 sequences have been introduced into their genome or homologous recombinant animals in which endogenous Tango-77
35 sequences have been altered. Such animals are useful for

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studying the function and/or activity of Tango-77 and for identifying and/or evaluating modulators of Tango-77 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous Tango-77 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing Tango-77-encoding nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The Tango-77 cDNA sequence e.g., that of (SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6; SEQ ID NO:10 or the cDNA of ATCC 98807) can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of the human Tango-77 gene, such as a mouse Tango-77 gene, can be isolated based on hybridization to the human Tango-77 cDNA and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency

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of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the Tango-77 transgene to direct expression of Tango-77 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the Tango-77 transgene in its genome and/or expression of Tango-77 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding Tango-77 can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a Tango-77 gene (e.g., a human or a non-human homolog of the Tango-77 gene, e.g., a murine Tango-77 gene) into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the Tango-77 gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous Tango-77 gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous Tango-77 gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby

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alter the expression of the endogenous Tango-77 protein). In the homologous recombination vector, the altered portion of the Tango-77 gene is flanked at its 5' and 3' ends by additional nucleic acid of the Tango-77 gene to
5 allow for homologous recombination to occur between the exogenous Tango-77 gene carried by the vector and an endogenous Tango-77 gene in an embryonic stem cell. The additional flanking Tango-77 nucleic acid is of sufficient length for successful homologous recombination
10 with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic
15 stem cell line (e.g., by electroporation) and cells in which the introduced Tango-77 gene has homologously recombined with the endogenous Tango-77 gene are selected (see, e.g., Li et al. (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal
20 (e.g., a mouse) to form aggregation chimeras (see, e.g., Bradley in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and
25 the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing
30 homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

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In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al. (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut et al. (1997) *Nature* 385:810-813 and PCT Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

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IV. Pharmaceutical Compositions

The Tango-77 nucleic acid molecules, Tango-77 proteins, and anti-Tango-77 antibodies (also referred to herein as "active compounds") of the invention can be
5 incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is
10 intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active
15 substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

20 A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, (e.g. intravenous, intradermal, subcutaneous) (e.g., oral inhalation), transdermal
25 (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene
30 glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as
35 acetates, citrates or phosphates and agents for the

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adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable
5 syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable
10 solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be
15 fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing,
20 for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance
25 of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid,
30 thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including

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in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a Tango-77 protein or anti-Tango-77 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a

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glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

5 For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

10 Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and
15 include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For
transdermal administration, the active compounds are
20 formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention
25 enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and
30 microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to
35 those skilled in the art. The materials can also be

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obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as
5 pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or
10 parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active
15 compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the
20 particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors.
25 Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection (see, e.g., Chen et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the
30 gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g.
35 retroviral vectors, the pharmaceutical preparation can

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include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with
5 instructions for administration.

V. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening
10 assays; b) detection assays (e.g., chromosomal mapping, tissue typing, forensic biology); c) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenomics); and d) methods of treatment (e.g., therapeutic and prophylactic). A
15 Tango-77 protein interacts with other cellular proteins and can thus be used for regulation of inflammation. The polypeptides of the invention can be used in assays to determine biological activity. For example, they could be used in a panel of proteins for high-throughput
20 screening.

The isolated nucleic acid molecules of the invention can be used to express Tango-77 protein (e.g., via a recombinant expression vector in a host cell in gene therapy applications), to detect Tango-77 mRNA
25 (e.g., in a biological sample) or a genetic lesion in a Tango-77 gene, and to modulate Tango-77 activity. In addition, the Tango-77 proteins can be used to screen drugs or compounds which modulate the Tango-77 activity or expression as well as to treat disorders characterized
30 by insufficient or excessive production of Tango-77 protein or production of Tango-77 protein forms which have decreased or aberrant activity compared to Tango-77 wild type protein. In addition, the anti-Tango-77

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antibodies of the invention can be used to detect and isolate Tango-77 proteins and modulate Tango-77 activity.

This invention further pertains to novel agents identified by the above-described screening assays and
5 uses thereof for treatments as described herein.

A. Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents
10 (e.g., peptides, peptidomimetics, small molecules or other drugs) which bind to Tango-77 proteins or have a stimulatory or inhibitory effect on, for example, Tango-77 expression or Tango-77 activity.

Examples of methods for the synthesis of molecular
15 libraries can be found in the art, for example in:

DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6909;
Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422;
Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et
al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew.*
20 *Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew.*
Chem. Int. Ed. Engl. 33:2061; and Gallop et al. (1994) *J.*
Med. Chem. 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Bio/Techniques* 13:412-
25 421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent Nos. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or phage (Scott and Smith
30 (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici (1991) *J. Mol. Biol.* 222:301-310).

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In another embodiment, an assay is used to determine the ability of the test compound to modulate the activity of Tango-77 or a biologically active portion thereof, for example, by determining the ability of the Tango-77 protein to bind to or interact with a Tango-77 target molecule. As used herein, a "target molecule" is a molecule with which a Tango-77 protein binds or interacts in nature, for example, a molecule on the surface of a cell. A Tango-77 target molecule can be a non-Tango-77 molecule or a Tango-77 protein or polypeptide of the present invention. In one embodiment, a Tango-77 target molecule is a component of a signal transduction pathway, for example, Tango-77 may bind to a IL-1 receptor or another receptor thereby blocking the receptor and inhibiting future signal transduction. Determining the ability of the Tango-77 protein to bind to or interact with a Tango-77 target molecule can be accomplished by one of the methods described above. In a preferred embodiment, determining the ability of the Tango-77 protein to bind to or interact with a Tango-77 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+} , diacylglycerol, IP3, etc.), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (e.g., a Tango-77-responsive regulatory element operably linked to a nucleic acid encoding a detectable marker, e.g. luciferase), or detecting a cellular response, for example, inflammation.

In yet another embodiment, an assay of the present invention is a cell-free assay comprising contacting a Tango-77 protein or biologically active portion thereof with a test compound and determining the ability of the

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test compound to bind to the Tango-77 protein or biologically active portion thereof. Binding of the test compound to the Tango-77 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the Tango-77 protein or biologically active portion thereof with a known compound which binds Tango-77 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a Tango-77 protein, wherein determining the ability of the test compound to interact with a Tango-77 protein comprises determining the ability of the test compound to preferentially bind to Tango-77 or biologically active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-free assay comprising contacting Tango-77 protein or biologically active portion thereof with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the Tango-77 protein or biologically active portion thereof. Determining the ability of the test compound to modulate the activity of Tango-77 can be accomplished, for example, by determining the ability of the Tango-77 protein to bind to a Tango-77 target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of Tango-77 can be accomplished by determining the ability of the Tango-77 protein to further modulate a Tango-77 target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as previously described.

In yet another embodiment, the cell-free assay comprises contacting the Tango-77 protein or biologically

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active portion thereof with a known compound which binds Tango-77 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a Tango-77 protein, wherein determining the ability of the test compound to interact with a Tango-77 protein comprises determining the ability of the Tango-77 protein to preferentially bind to or modulate the activity of a Tango-77 target molecule.

10 It is possible that membrane-bound forms of Tango-77 exist. The cell-free assays of the present invention are amenable to use of both the forms Tango-77. In the case of cell-free assays comprising a membrane-bound form of Tango-77, it may be desirable to utilize a
15 solubilizing agent such that the membrane-bound form of Tango-77 is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide,
20 Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-
25 dimethyl-3-ammonio-1-propane sulfonate.

 In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either Tango-77 or its target molecule to facilitate separation of complexed from uncomplexed forms
30 of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to Tango-77, or interaction of Tango-77 with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for
35 containing the reactants. Examples of such vessels

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include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For
5 example, glutathione-S-transferase/ Tango-77 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical Co.; St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined
10 with the test compound or the test compound and either the non-adsorbed target protein or Tango-77 protein, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or
15 microtitre plate wells are washed to remove any unbound components and complex formation is measured either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of Tango-77 binding or activity
20 determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either Tango-77 or its target molecule can be immobilized utilizing conjugation of
25 biotin and streptavidin. Biotinylated Tango-77 or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL), and immobilized in the wells of streptavidin-coated
30 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with Tango-77 or target molecules but which do not interfere with binding of the Tango-77 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or Tango-77
35 trapped in the wells by antibody conjugation. Methods

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for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the Tango-77 or target molecule, as well as
5 enzyme-linked assays which rely on detecting an enzymatic activity associated with the Tango-77 or target molecule.

In another embodiment, modulators of Tango-77 expression are identified in a method in which a cell is contacted with a candidate compound and the expression of
10 Tango-77 mRNA or protein in the cell is determined. The level of expression of Tango-77 mRNA or protein in the presence of the candidate compound is compared to the level of expression of Tango-77 mRNA or protein in the absence of the candidate compound. The candidate
15 compound can then be identified as a modulator of Tango-77 expression based on this comparison. For example, when expression of Tango-77 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence,
20 the candidate compound is identified as a stimulator of Tango-77 mRNA or protein expression. Alternatively, when expression of Tango-77 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate
25 compound is identified as an inhibitor of Tango-77 mRNA or protein expression. The level of Tango-77 mRNA or protein expression in the cells can be determined by methods described herein for detecting Tango-77 mRNA or protein.

30 In yet another aspect of the invention, the Tango-77 proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054;
35 Bartel et al. (1993) *Bio/Techniques* 14:920-924; Iwabuchi

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et al. (1993) *Oncogene* 8:1693-1696; and PCT Publication No. WO 94/10300), to identify other proteins, which bind to or interact with Tango-77 ("Tango-77-binding proteins" or "Tango-77-bp") and modulate Tango-77 activity. Such
5 Tango-77-binding proteins are also likely to be involved in the propagation of signals by the Tango-77 proteins as, for example, upstream or downstream elements of the Tango-77 pathway.

The two-hybrid system is based on the modular
10 nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for Tango-77 is fused to a gene encoding the DNA binding domain of a known
15 transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If
20 the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an Tango-77-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ)
25 which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes
30 the protein which interacts with Tango-77.

This invention further pertains to novel agents identified by the above-described screening assays and uses thereof for treatments as described herein.

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B. Detection Assays

Portions or fragments of the cDNA sequence identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, the sequence can be used to: (i) map the respective gene on a chromosome and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

1. Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome.

Accordingly, Tango-77 nucleic acid molecules described herein or fragments thereof, can be used to map the location of the Tango-77 gene(s) on a chromosome. The mapping of the Tango-77 sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, a Tango-77 gene can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the Tango-77 sequences. Computer analysis of Tango-77 sequences can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the Tango-77 sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (e.g., human and

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mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow (because they lack a particular enzyme) but in which human cells can, the one human chromosome that contains the gene encoding the needed enzyme, will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. (D'Eustachio et al. (1983) *Science* 220:919-924). Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the Tango-77 sequences to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be used to map a Tango-77 sequence to its chromosome include *in situ* hybridization (described in Fan et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6223-27), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been blocked in metaphase by a chemical, e.g., colcemid that disrupts the mitotic spindle. The

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chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be
5 used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases
10 will suffice to get good results at a reasonable amount of time. For a review of this technique, see Verma et al. (Human Chromosomes: A Manual of Basic Techniques (Pergamon Press, New York, 1988)).

Reagents for chromosome mapping can be used
15 individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding
20 sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the
25 sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the
30 same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, e.g., Egeland et al. (1987) Nature 325:783-787.

Moreover, differences in the DNA sequences between
35 individuals affected and unaffected with a disease

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associated with the Tango-77 gene can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

2. Tissue Typing

The Tango-77 sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

Furthermore, the sequences of the present invention can be used to provide an alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the Tango-77 sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the

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sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals and from tissue. The Tango-77 sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences of SEQ ID NO:1 can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NO:3, SEQ ID NO:6, or SEQ ID NO:10 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

If a panel of reagents from Tango-77 sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

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3. Use of Partial Tango-77 Sequences in Forensic Biology

DNA-based identification techniques can also be used in forensic biology. Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

The sequences of the present invention can be used to provide polynucleotide reagents, e.g., PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (i.e. another DNA sequence that is unique to a particular individual). As mentioned above, actual base sequence information can be used for identification as an accurate alternative to patterns formed by restriction enzyme generated fragments.

Sequences targeted to noncoding regions of SEQ ID NO:1 are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of polynucleotide reagents include the Tango-77 sequences or portions thereof, e.g., fragments derived from the noncoding regions of SEQ ID NO:1 having a length of at least 20 or 30 bases.

The Tango-77 sequences described herein can further be used to provide polynucleotide reagents, e.g., labeled or labelable probes which can be used in, for

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example, an *in situ* hybridization technique, to identify a specific tissue, e.g., brain tissue. This can be very useful in cases where a forensic pathologist is presented with a tissue of unknown origin. Panels of such Tango-77 probes can be used to identify tissue by species and/or by organ type.

In a similar fashion, these reagents, e.g., Tango-77 primers or probes can be used to screen tissue culture for contamination (i.e., screen for the presence of a mixture of different types of cells in a culture).

C. Predictive Medicine

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining Tango-77 protein and/or nucleic acid expression as well as Tango-77 activity, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant Tango-77 expression or activity. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with Tango-77 protein, nucleic acid expression or activity. For example, mutations in a Tango-77 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with Tango-77 protein, nucleic acid expression or activity.

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Another aspect of the invention provides methods for determining Tango-77 protein, nucleic acid expression or Tango-77 activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds) on the expression or activity of Tango-77 in clinical trials.

These and other agents are described in further detail in the following sections.

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of Tango-77 in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting Tango-77 protein or nucleic acid (e.g., mRNA, genomic DNA) that encodes Tango-77 protein such that the presence of Tango-77 is detected in the biological sample. A preferred agent for detecting Tango-77 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to Tango-77 mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length Tango-77 nucleic acid, such as the nucleic acid of SEQ ID NO: 1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent

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conditions to Tango-77 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting Tango-77 protein is an antibody capable of binding to Tango-77 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect Tango-77 mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of Tango-77 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of Tango-77 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of Tango-77 genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of Tango-77 protein include introducing into a subject a labeled anti-Tango-77 antibody. For example, the antibody can be

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labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting Tango-77 protein, mRNA, or genomic DNA, such that the presence of Tango-77 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of Tango-77 protein, mRNA or genomic DNA in the control sample with the presence of Tango-77 protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of Tango-77 in a biological sample (a test sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing a disorder associated with aberrant expression of Tango-77 (e.g., an immunological disorder). For example, the kit can comprise a labeled compound or agent capable of detecting Tango-77 protein or mRNA in a biological sample and means for determining the amount of Tango-77 in the sample (e.g., an anti-Tango-77 antibody or an oligonucleotide probe which binds to DNA encoding Tango-77, e.g., SEQ ID NO:1 or SEQ ID NO:3 or SEQ ID NO:6, or SEQ ID NO:10). Kits may also include instruction for observing that the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of Tango-77 if the

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amount of Tango-77 protein or mRNA is above or below a normal level.

For antibody-based kits, the kit may comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to Tango-77 protein; and, optionally (2) a second, different antibody which binds to Tango-77 protein or the first antibody and is conjugated to a detectable agent.

For oligonucleotide-based kits, the kit may comprise, for example: (1) an oligonucleotide, e.g., a detectably labelled oligonucleotide, which hybridizes to a Tango-77 nucleic acid sequence or (2) a pair of primers useful for amplifying a Tango-77 nucleic acid molecule;

The kit may also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit may also comprise components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit may also contain a control sample or a series of control samples which can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container and all of the various containers are within a single package along with instructions for observing whether the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of Tango-77.

2. Prognostic Assays

The methods described herein can furthermore be utilized as diagnostic or prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with aberrant Tango-77 expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or

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at risk of developing a disorder associated with aberrant expression or activity. Thus, the present invention provides a method in which a test sample is obtained from a subject and Tango-77 protein or nucleic acid (e.g., mRNA, genomic DNA) is detected, wherein the presence of Tango-77 protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant Tango-77 expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (e.g., serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant Tango-77 expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with a specific agent or class of agents (e.g., agents of a type which decrease Tango-77 activity). Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant Tango-77 expression or activity in which a test sample is obtained and Tango-77 protein or nucleic acid is detected (e.g., wherein the presence of Tango-77 protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant Tango-77 expression or activity).

The methods of the invention can also be used to detect genetic lesions or mutations in a Tango-77 gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant

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inflammation. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion or mutation characterized by at least one of an alteration affecting
5 the integrity of a gene encoding a Tango-77-protein, or the mis-expression of the Tango-77 gene. For example, such genetic lesions or mutations can be detected by ascertaining the existence of at least one of: 1) a deletion of one or more nucleotides from a Tango-77 gene;
10 2) an addition of one or more nucleotides to a Tango-77 gene; 3) a substitution of one or more nucleotides of a Tango-77 gene; 4) a chromosomal rearrangement of a Tango-77 gene; 5) an alteration in the level of a messenger RNA transcript of a Tango-77 gene; 6) an
15 aberrant modification of a Tango-77 gene, such as of the methylation pattern of the genomic DNA; 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a Tango-77 gene; 8) a non-wild type level of a Tango-77-protein; 9) an allelic loss of a Tango-77
20 gene, and 10) an inappropriate post-translational modification of a Tango-77-protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions or mutations in a Tango-77 gene. A preferred biological sample is a
25 peripheral blood leukocyte sample isolated by conventional means from a subject.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g., U.S. Patent Nos. 4,683,195 and
30 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) *Science* 241:1077-1080; and Nakazawa et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for
35 detecting point mutations in the Tango-77-gene (see,

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e.g., Abravaya et al. (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a Tango-77 gene under conditions such that hybridization and amplification of the Tango-77-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) *Bio/Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in a Tango-77 gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA

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indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, e.g., U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme
5 cleavage site.

In other embodiments, genetic mutations in Tango-77 can be identified by hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of
10 oligonucleotides probes (Cronin et al. (1996) *Human Mutation* 7:244-255; Kozal et al. (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in Tango-77 can be identified in two-dimensional arrays containing light-generated DNA probes as described in Cronin et al.
15 *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification
20 of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel
25 probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the Tango-77 gene and detect mutations
30 by comparing the sequence of the sample Tango-77 with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a
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variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) *Bio/Techniques* 19:448), including sequencing by mass spectrometry (see, e.g., PCT Publication No. WO 94/16101; 5 Cohen et al. (1996) *Adv. Chromatogr.* 36:127-162; and Griffin et al. (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in the Tango-77 gene include methods in which protection from 10 cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers et al. (1985) *Science* 230:1242). In general, the technique of "mismatch cleavage" entails providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the 15 wild-type Tango-77 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and 20 sample strands. RNA/DNA duplexes can be treated with RNase to digest mismatched regions, and DNA/DNA hybrids can be treated with S1 nuclease to digest mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium 25 tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, e.g., Cotton et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:4397; Saleeba et al. (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the 30 control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize 35 mismatched base pairs in double-stranded DNA (so called

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"DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in Tango-77 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the
5 thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a Tango-77 sequence, e.g., a wild-type Tango-77 sequence, is hybridized to a cDNA or other DNA product
10 from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, e.g., U.S. Patent No. 5,459,039.

In other embodiments, alterations in
15 electrophoretic mobility will be used to identify mutations in Tango-77 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) *Proc.*
20 *Natl. Acad. Sci. USA* 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144; Hayashi (1992) *Genet Anal Tech Appl* 9:73-79). Single-stranded DNA fragments of sample and control Tango-77 nucleic acids will be denatured and allowed to renature. The secondary structure of single-
25 stranded nucleic acids varies according to sequence, and the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by
30 using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in

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electrophoretic mobility (Keen et al. (1991) *Trends Genet* 7:5).

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al. (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys. Chem.* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) *Nature* 324:163); Saiki et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al. (1989) *Nucleic*

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Acids Res. 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition, it may be desirable to
5 introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al. (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany
10 (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of
15 amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used,
20 e.g., in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a Tango-77 gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which Tango-77 is
25 expressed may be utilized in the prognostic assays described herein.

3. Pharmacogenomics

Agents, or modulators which have a stimulatory or
30 inhibitory effect on Tango-77 activity (e.g., Tango-77 gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders (e.g., acute or chronic inflammation and asthma)
35 associated with aberrant Tango-77 activity. In

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conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens.

Accordingly, the activity of Tango-77 protein, expression of Tango-77 nucleic acid, or mutation content of Tango-77 genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Linder (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-

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malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both
5 the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug
10 effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is
15 different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience
20 exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM shows no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other
25 extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of Tango-77 protein, expression
30 of Tango-77 nucleic acid, or mutation content of Tango-77 genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping
35 of polymorphic alleles encoding drug-metabolizing enzymes

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to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a Tango-77 modulator, such as a modulator identified by one of the exemplary screening assays described herein.

4. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (e.g., drugs, compounds) on the expression or activity of Tango-77 (e.g., the ability to modulate aberrant inflammation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent, as determined by a screening assay as described herein, to increase Tango-77 gene expression, increase protein levels, or upregulate Tango-77 activity, can be monitored in clinical trials of subjects exhibiting decreased Tango-77 gene expression, decreased protein levels, or downregulated Tango-77 activity.

Alternatively, the effectiveness of an agent, as determined by a screening assay, to decrease Tango-77 gene expression, decrease protein levels, or downregulate Tango-77 activity, can be monitored in clinical trials of subjects exhibiting increased Tango-77 gene expression, increased protein levels, or upregulated Tango-77 activity.

For example, and not by way of limitation, genes, including Tango-77, that are modulated in cells by treatment with an agent (e.g., compound, drug or small molecule) which modulates Tango-77 activity (e.g., as identified in a screening assay described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared

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and analyzed for the levels of expression of Tango-77 and other genes implicated in the disorder. The levels of gene expression (i.e., a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as
5 described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of Tango-77 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of
10 the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In a preferred embodiment, the present invention
15 provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) comprising the
20 steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a Tango-77 protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples
25 from the subject; (iv) detecting the level of expression or activity of the Tango-77 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the Tango-77 protein, mRNA, or genomic DNA in the pre-administration sample
30 with the Tango-77 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or
35 activity of Tango-77 to higher levels than detected,

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i.e., to increase the effectiveness of the agent.
Alternatively, decreased administration of the agent may
be desirable to decrease expression or activity of
Tango-77 to lower levels than detected, i.e., to decrease
5 the effectiveness of the agent.

C. Methods of Treatment

The present invention provides for both
prophylactic and therapeutic methods of treating a
subject at risk of (or susceptible to) developing or
10 having a disorder associated with aberrant Tango-77
expression or activity. Alternatively, disorders
associated with aberrant IL-1 production can be treated
with Tango-77. Such disorders include acute and chronic
inflammation, asthma, some classes of arthritis,
15 autoimmune diabetes, systemic lupus erythematosus and
inflammatory bowel disease.

1. Prophylactic Methods

In one aspect, the invention provides a method for
preventing in a subject, a disease or condition
20 associated with an aberrant Tango-77 expression or
activity (or aberrant IL-1 expression or activity), by
administering to the subject an agent which modulates
Tango-77 expression or at least one Tango-77 activity.
Subjects at risk for a disease which is caused or
25 contributed to by aberrant Tango-77 expression or
activity can be identified by, for example, any or a
combination of diagnostic or prognostic assays as
described herein. Administration of a prophylactic agent
can occur prior to the manifestation of symptoms
30 characteristic of the Tango-77 aberrancy, such that a
disease or disorder is prevented or, alternatively,
delayed in its progression. Depending on the type of
Tango-77 aberrancy, for example, a Tango-77 agonist or
Tango-77 antagonist agent can be used for treating the

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subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

Another aspect of the invention pertains to methods of modulating Tango-77 expression or activity for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of Tango-77 protein activity associated with the cell. An agent that modulates Tango-77 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of a Tango-77 protein, a peptide, a Tango-77 peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more of the biological activities of Tango-77 protein. Examples of such stimulatory agents include active Tango-77 protein and a nucleic acid molecule encoding Tango-77 that has been introduced into the cell. In another embodiment, the agent inhibits one or more of the biological activities of Tango-77 protein. Examples of such inhibitory agents include antisense Tango-77 nucleic acid molecules and anti-Tango-77 antibodies. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a Tango-77 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) Tango-77 expression or activity. In another embodiment, the method involves

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administering a Tango-77 protein or nucleic acid molecule as therapy to compensate for reduced or aberrant Tango-77 expression or activity.

Stimulation of Tango-77 activity is desirable in situations in which Tango-77 is abnormally downregulated and/or in which increased Tango-77 activity is likely to have a beneficial effect. Conversely, inhibition of Tango-77 activity is desirable in situations in which Tango-77 is abnormally upregulated and/or in which decreased Tango-77 activity is likely to have a beneficial effect.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLES

Example 1: Isolation and Characterization of Human Tango-77 cDNAs

Cytokine genes IL-1 α , IL-1 β and IL-1ra have been found to be closely clustered on chromosome 2, i.e., IL-1 α , IL-1 β and IL-1ra are located within 450 kb of each other. BAC clones containing IL-1 α and IL-1 β were used to identify other proximal unknown cytokine genes. To do this, a BAC clone containing IL-1 α and IL-1 β was selected from a BAC library (Research Genetics, Huntsville, Alabama) using specific primers designed against IL-1 α and IL-1 β . The DNA from the BAC was extracted and used to make a random-sheared genomic library. From this BAC library, 4000 clones were selected for sequencing. The resulting genomic sequences were then assembled into contigs and used to screen proprietary and public data bases. One genomic contig was found to contain two

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segments of sequences which resemble IL-1ra. These two segments are potential exons of Tango-77 gene.

Two PCR primers were then designed from the two potential exons and used to screen a panel of cDNA libraries for the expression of a Tango-77 message. A cDNA library from TNF- α treated human lung epithelia showed a positive band of the predicted size (i.e., if the two exons are spliced together). Using the PCR fragment as a probe, a single cDNA clone was isolated from the same library. This cDNA contains an insert of 989 bp. The cDNA clone contains three possible open reading frames. The first open reading frame encompasses 534 nucleotides (nucleotides 356-889 of SEQ ID NO:1; SEQ ID NO:3) and encodes a 178 amino acid protein (SEQ ID NO:2). This protein may include a predicted signal sequence of about 63 amino acids (from amino acid 1 to about amino acid 63 of SEQ ID NO:2 (SEQ ID NO:4)) and a predicted mature protein of about 115 amino acids (from about amino acid 64 to amino acid 178 of SEQ ID NO:2 (SEQ ID NO:5)).

The second putative nucleotide open reading frame encompasses 498 nucleotides (nucleotides 389-889 of SEQ ID NO:1; SEQ ID NO:6) and encodes a 167 amino acid protein (SEQ ID NO:7). This protein includes a predicted signal sequence of about 52 amino acids (from amino acid 1 to about amino acid 52 of SEQ ID NO:7 (SEQ ID NO:8)) and a predicted mature protein of about 115 amino acids (from about amino acid 53 to amino acid 167 of SEQ ID NO:7 (SEQ ID NO:9)).

The third open reading frame (nucleotides 372-889 of SEQ ID NO:1; SEQ ID NO:10) encompasses 408 nucleotides and encodes a 136 amino acid protein (SEQ ID NO:11). This protein includes a predicted signal sequence of about 21 amino acids (from amino acid 1 to about amino acid 21 of SEQ ID NO:11 (SEQ ID NO:12)) and a predicted

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mature protein of about 115 amino acids (from about amino acid 22 to amino acid 136 of SEQ ID NO:11 (SEQ ID NO:13)).

Tango-77 is predicted to be 35% identical to human IL-1ra at the amino acid level.

Example 2: Expression of Tango-77 mRNA in Human Tissues

The expression of Tango-77 was analyzed using Northern blot hybridization. A PCR generated 989 bp Tango-77 product was radioactively labeled with ³²P-dCTP using the Prime-It kit (Stratagene; La Jolla, CA) according to the instructions of the supplier. Filters containing human mRNA (MTNI and MTNII: Clontech; Palo Alto, CA) were probed in ExpressHyb hybridization solution (Clontech) and washed at high stringency according to manufacturer's recommendations.

Tango-77 mRNA was not detected in any unstimulated tissues (brain, liver, spleen, skeletal muscle, testis, pancreas, heart, kidney and peripheral blood leukocytes) mRNA on Clontech Northern blots.

Over 96 cDNA libraries were then tested for the presence of Tango-77 using PCR amplification. Only three libraries displayed a positive signal. These libraries were the TNF α -treated bronchoepithelium, TNF α -treated SSC cell line and anti-CD3-treated T cells.

Example 3: Characterization of Tango-77 Proteins

In this example, the predicted amino acid sequence of human Tango-77 protein was compared to the amino acid sequence of known protein IL-1ra. In addition, the molecular weight of the human Tango-77 proteins was predicted.

The human Tango-77 cDNA (Figure 1; SEQ ID NO:1) isolated as described above encodes a 178 amino acid protein (Figure 1; SEQ ID NO:2) or a 167 amino acid

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protein (Figure 1; SEQ ID NO:7) or a 136 amino acid protein (Figure 1; SEQ ID NO:11). The signal peptide prediction program SIGNALP Optimized Tool (Nielsen et al. (1997) *Protein Engineering* 10:1-6) predicted that

5 Tango-77 includes a 63 amino acid signal peptide (amino acid 1 to about amino acid 63 of SEQ ID NO:2 (SEQ ID NO:4)) preceding the 115 mature protein; or preceding the 115 mature protein (about amino acid 52 to amino acid 167 of SEQ ID NO:7 (SEQ ID NO:8)); or preceding the 115

10 mature protein (about amino acid 21 to amino acid 136 of SEQ ID NO:11;SEQ ID NO:12).

As shown in Figure 2, Tango-77 has a region of homology to IL-1ra (SEQ ID NO:14).

Mature Tango-77 has a predicted MW of about 13 kDa

15 and the predicted MW for the immature Tango-77 is 19.6 kDa, 18.5 kDa or 15.2 kDa, not including post-translational modifications.

Example 4: Preparation of Tango-77 Proteins

Recombinant Tango-77 can be produced in a variety

20 of expression systems. For example, the mature Tango-77 peptide can be expressed as a recombinant glutathione-S-transferase (GST) fusion protein in *E. coli* and the fusion protein can be isolated and characterized.

Specifically, as described above, Tango-77 can be fused

25 to GST and this fusion protein can be expressed in *E. coli* strain PEB199. Expression of the GST-Tango-77 fusion protein in PEB199 can be induced with IPTG. The recombinant fusion protein can be purified from crude bacterial lysates of the induced PEB199 strain by

30 affinity chromatography on glutathione beads.

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Example 5: Alternatively spliced forms of IL-1ra and
Tango-77

Computer program Procrustes (Gelfand et al., 1996, *Proc. Natl. Acad. Sci. USA*, 93:9061-9066) is an alignment
5 algorithm that predicts the presence of alternatively
spliced exons for a protein of interest in a stretch of
genomic DNA. Using the IL-1ra sequence, Procrustes was
used to search for the presence of additional sequences
that might encode for alternatively spliced forms of IL-
10 1ra in the two overlapping BAC genomic sequences (see
Fig. 3 and Fig. 4). Potential sequences that encode
variant exons for IL-1ra were identified. These
predicted exons aligned well with the N-terminal region
of IL-1ra, but were not present in Tango-77. The results
15 from Procrustes predicts the existence of more spliced
forms of IL-1ra.

Furthermore, Procrustes also predicted an
additional sequence in BAC1 and BAC2 that encodes an
alternatively spliced exon for Tango-77 (T77-procrustes;
20 Fig. 5). This predicted splice variant form of Tango-77,
T77-procrustes, was aligned with Tango-77 (Fig. 6) and
with IL-1ra and IL-1 β (Fig. 7).

PCR primers within this sequence can be used to
generate a product that can be used to screen a panel of
25 cDNA libraries using standard techniques. Suitable cDNA
libraries include libraries made from TNF α -treated
bronchoepithelium, TNF α -treated SSC cell line and anti-
CD3-treated T cells. The resulting cDNA clone(s) can be
isolated from the library and sequenced to identify
30 additional Tango-77 cDNAs.

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Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific
5 embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:

- a) a nucleic acid molecule comprising a
5 nucleotide sequence which is at least 45% identical to the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, or a complement thereof;
- 10 b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, or a complement thereof;
- 15 c) nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the
20 plasmid deposited with ATCC as Accession Number 98807;
- d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID
25 NO:12, SEQ ID NO:13, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or the polypeptide encoded by the cDNA insert of the plasmid
30 deposited with ATCC as Accession Number 98807; and
- e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9,

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SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, wherein the nucleic acid molecule hybridizes to a nucleic acid
5 molecule comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10, or the complement thereof under stringent conditions.

2. The isolated nucleic acid molecule of claim 1, which is selected from the group consisting of:

10 a) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, or SEQ ID NO:10 or the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, or a complement thereof; and

15 b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the
20 plasmid deposited with ATCC as Accession Number 98807.

3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

4. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous
25 polypeptide.

5. A host cell containing the nucleic acid molecule of claim 1.

6. The host cell of claim 5 which is a mammalian host cell.

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7. A non-human mammalian host cell containing the nucleic acid molecule of claim 1.

8. An isolated polypeptide selected from the group consisting of:

5 a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID
10 NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:13.

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8,
15 SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule
20 comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:10 or the complement thereof under stringent conditions;

c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is
25 at least 55% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, or SEQ ID NO:10.

9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:2, SEQ ID
30 NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807.

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10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

11. An antibody which selectively binds to a polypeptide of claim 8.

5 12. A method for producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID
10 NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807;

b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID
15 NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807, wherein the fragment comprises at least 15 contiguous amino acids
20 of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Accession Number 98807; and

25 c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or an amino acid sequence encoded by the cDNA insert of the
30 plasmid deposited with ATCC as Accession Number 98807, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid sequence of

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SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, or SEQ ID NO:10
under stringent conditions;

comprising culturing the host cell of claim 5
under conditions in which the nucleic acid molecule is
5 expressed.

13. A method for detecting the presence of a
polypeptide of claim 8 in a sample, comprising:

- a) contacting the sample with a compound which
selectively binds to a polypeptide of claim 8; and
- 10 b) determining whether the compound binds to the
polypeptide in the sample.

14. The method of claim 13, wherein the compound
which binds to the polypeptide is an antibody.

15. A kit comprising a compound which selectively
15 binds to a polypeptide of claim 8 and instructions for
use.

16. A method for detecting the presence of a
nucleic acid molecule of claim 1 in a sample, comprising
the steps of:

- 20 a) contacting the sample with a nucleic acid
probe or primer which selectively hybridizes to the
nucleic acid molecule; and
-

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18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

19. A method for identifying a compound which
5 binds to a polypeptide of claim 8 comprising the steps of:

- a) contacting a polypeptide, or a cell expressing a polypeptide of claim 8 with a test compound; and
- 10 b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- 15 a) detection of binding by direct detecting of test compound/polypeptide binding;
- b) detection of binding using a competition binding assay; and
- c) detection of binding using an assay for
20 Tango-77-mediated signal transduction.s

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting a polypeptide or a cell expressing a polypeptide of claim 8 with a compound which binds to the polypeptide in a
25 sufficient concentration to modulate the activity of the polypeptide.

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22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8, comprising:

- a) contacting a polypeptide of claim 8 with a
5 test compound; and
- b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

GTGACCCACGCGTCCGCAGACGTCTACCTGGGGGTCCCGTCTGCGCTCCCGGGATGGAAAACGCCCAGGGGAAACTTA 79
GGCAGGCGAGCGGACGGGCACCTCCCGCGGGACGAACTCACTCGGTGGCCTCCTACTTCCCCGGCCGTGTTCCAACGCC 158
TGAGAATAACGGGAACAGCGGTTCGTACTCACCAGACAGCGGCAGCAGCGGCCTCTCTCAATTGGGCAAAGCACTCCAGAC 237
CTTTTGGGAAGAGTGACACCAAAGGCAAGCACCTGCTTGGCAGGCCCTCAGCTTCTACGCAAGTATAAGTCTTGGACTT 316
CATTCCATTTTCTGTTGAGTAATAAACTCAACGTTGAAA M S F V G E N S G V 10
ATG TCC TTT GTG GGG GAG AAC TCA GGA GTG 385
K M G S E D W E K D E P Q C C L E D P A 30
AAA ATG GGC TCT GAG GAC TGG GAA AAA GAT GAA CCC CAG TGC TGC TTA GAA GAC CCG GCT 445
G S P L E P G P S L P T M N F V H T K I 50
GGA AGC CCC CTG GAA CCA GGC CCA AGC CTC CCC ACC ATG AAT TTT GTT CAC ACA AAG ATC 505
F F A L A S S L S S A S A E K G S P I L 70
TTC TTT GCA TTA GCC TCA TCC TTG AGC TCA GCC TCT GCG GAG AAA GGA AGT CCG ATT CTC 565
L S Y S K G E F C L Y C D K D K G Q S H 90
CTG GGG CTC TCT AAA GGG GAG TTT TGT CTC TAC TGT GAC AAG GAT AAA GGA CAA AGT CAT 625
P S L Q L K K E K L M K L A A Q K E S A 110
CCA TCC CTT CAG CTG AAG AAG GAG AAA CTG ATG AAG CTG GCT GCC CAA AAG GAA TCA GCA 685
R R P F I F Y R A Q Y G S W N M L E S A 130
CGC CGG CCC TTC ATC TTT TAT AGG GCT CAG GTG GGC TCC TGG AAC ATG CTG GAG TCG GCG 745
A H P G W F I C T S C N C N E P V G V T 150
GCT CAC CCC GGA TGG TTC ATC TGC ACC TCC TGC AAT TGT AAT GAG CCT GTT GGG GTG ACA 805
D K F E N R K H I E F S F Q P V C K A E 170
GAT AAA TTT GAG AAC AGG AAA CAC ATT GAA TTT TCA TTT CAA CCA GTT TGC AAA GCT GAA 865
M S P S E V S D * 179
ATG AGC CCC AGT GAG GTC AGC GAT TAG 892
GAAACTGCCCCATTGAACGCCTTCCTCGCTAATTTGAACTAATTGTATAAAAACACCAAACCTGCTCACTAAAAAAA 971
AAAAAAAAGGGCGGCCGC 989

Fig. 1

1 50
IL1ra-human MEICRGLRSH LITLLFLFH SETICRPSGR KSSKMQAFRI WDVNQKTFYL
T77-human ~~~~~~
IL1b-human ~~~~~~APVRSI NCTLRDSQQK SLVMSGPYEL
Consensus ~~~~~~

51 100
IL1ra-human RNNQLVAGYL QGPNVNLEEK IDVVPTEPH. ALFLGIHGK MCLSCVKSGD
T77-human ~~~~MNFVHT KIFFALASSL SSASAEGKS. PILLGVSKGE FCLYCDKDKG
IL1b-human KALHLQGQDM EQQVVFMSF VQGEESNDKI PVALGLKEKN LYLSCVLKDD
Consensus ~~~~~~LG~~~~~L-C~~~~~

101 150
IL1ra-human ETR..LQLEA VNITDLSNR KQDKR.FAFI RDSGPTTSF ESAACPGWFL
T77-human QSHPSLQLKK EKLMLAAQK ESARRPFIFY RAQVGSWNML ESAAHPEWFI
IL1b-human K..PTLQLES VDPKNYP..K KMEKRFFVN KIEINNKLFE ESAQFPNWYI
Consensus ~~~~~~LQL~~~~~F-F~~~~~ESA--P-W~~~~~

151 192
IL1ra-human CTAMEADQPV SLTNMPDEGV MVTKFYFQED E~~~~~
T77-human CTSCNCNEPV GVTDKFENRK HI.EFSFPV CKAEMSPSEV SD
IL1b-human STSQAENMPV FLGGT.KGGQ DITDFTMQFV SS~~~~~
Consensus -T~~~~~PV ~~~~~~F--Q~~~~~

FIG. 2

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>Contig1

GAAGTGAAGATATAATGTATAGTAGTAATATATAATGTTAGGTGAATTAA
AGGAAATAGAATATATTGGGGAGTAATTATGGGTGTAAAGAAATATAGTA
GGGAAGTATTTAGATTTGAGAAAAAAGGAATTTAGTGTAGGTGAA
NAATAAAAGNANAAGGTTAAAAATTAAAAAATTAAATATAAATAAAT
AAATAAAAAATAAAAAATAAAAAATTTAAAAAATTAAAAAATATAA
AAAAATAAGAAATGGAAGTGGATTCTTAGAAAAAAGAAAGTAAGGTGA
TATGAGGAGATAGAGAGGATGTGGTGTGAGATGATTGGTTTAATTAGAAA
ATAGGTTTTGAATAGAGTGGGAAAGTAGAGTTTTGGTAAATGTGGGGGGA
AGAGGGTAATGTTGTTTGAAGTGAAGAAAAAATGGTATATTTTTATAAAA
TAATGAGGAAAGTGTGTGAAAAAATTATTGGGATTTGGGAAGGTGAT
ATATAAGTTGTGGAAATTTGGGGGGTGGGGTTTATTAGGATTAAAAA
GTTATTTAAAGAATGAAATGAATTTTTGTTTGTAAATTTGGGGATAAGAA
ATTAATGTTTAGAAAGAAAGGGAAAAAATTGAAGAAAAAATTTAGATTT
TGGAAATTTAAAAATATTGTGGGTGTAAATAGGAAGGATTTTAAAGGTA
ATTGTGGAAGGGATTTGTGTGGAAATAATAGGGAGAAAAAATGGGG

>Contig2

GCATCTAAGTGGAGCCTGCATTATTACAGATTTAGCATCACCAAAGTCTA
AACAAATTAGACTGACTAAGGCAGAACTGCCCTTATGACAGCAGACATAAG
AAGGAAAAGGCCAAAACACTGTGTTAAAAATTATCCAAATGTGAGGAAAA
GGCAAAGAGAGTAGGTGTGCCTTTTTAGTGTCTAAGCTGCCTGCCCCAAGG
GGCATCTGATGCTCTCAGGCAGGAGTCCACAAATTTTTTTTTGTAAAAGA
TCAGATAGTAAATCTTTTCAGCGTGAAGAGCATGAGGTCTCTGTCACAAA
TACTCAACCACCATTACAACATGAAAGCAGCCAACAGACAACACATGACA
AATGAGTGTGGCTGTGTTCCAGTAAATCTTGATTACAAAACAGGCAAGA
GGCCAGAGCTGACCCATGGGCCATAGTTTGCTGACCCCTTCTGTAAAGGA
AAGTATTTTTGTTTGACTTGCTGTTTACCATTGATTGAACACAAGGCTCT
GTAAAGTTACTTGTTAACTTGCAGAAGATTGATGAGTGGCAAGTAATTTT
TATTCACCAGAATATAAAATTATTTCTGTTTCAGTAGAAAAGATAAACCAA
CTGTGATATTATGGTCCTG

>Contig3

GGGGTGTCTGTCTACCATGTGCTCGCAGTTCTGTAATAAATGTTCTCTCA
AGATCCTTAAATCTCTTGGAAATTATAAAATATTGGAAAGAGAAGAAC
AGTTTTTAAATATATATATATATATATATTTTTTTTGAGATGGAGTCTT
GCTCTGTCTGTCAGGCTGGAGTGCAGTGGCGCAAACCTTGTTTCACCACAA
CCTCTGCCTCCCGGGTTCAAGCGATTCTTCTGCCTCAGCCTCCTGAGTAG
CTGGGACTACAGGCGCCCGCCACCACGCCCAGCTAATTTTTGTATTTTAA
GTAGAGACGAGGTTTTACTATGTTGGCTAGGCTGGTCTCAAACCTCCTGAC
CTTGATGATCTGCCCCGCTTGGCCTCCCAAAGTGCTGGGATTACAGGTGTG
AGCCACTGCACCTGGCCAGTTTTTTTAAATATATTTTTTAAAAACACTTGAA
TAAGAGTCAGTGTAAGTGAAGTTTAAAAATGCTTCACAGAACACCCAG
GGTTTACATTACAAGATTCTCACAACAAACCTATTGTAAAGGTGAGTAAG
GCATGTTATTACAGAGAAAAGTTTGGGAGCAAACTGTAAAAAATTATAT
TTTTGTTGTATTTTCTAAGAGAAAGAGTATTGTTATGTTCTCCTAACCTC
TGTTGATTACTACTTTAAGTGATTTCTTGGAGAGCACATGATGATCC

>Contig4

GCCGTTTCATAGAAAACCTGAAAGCAATAAGATGACTAGGTAAGCATGACAT
TTAAAAGGTATTCATGGGACGTGGTTACAAAACCAACTCACAACTAAAAA
GTCTTAGGACCTCTCGCTGACTTAGGAGCCTGATCCCAACTCTGAGAATG
ACTCAGTGTGTTACCCTGTGGCTAGTGTAGACCAATGATCCTGTCTCAGA
GTCAGTACCCAACAGCCCATATCAAGTACTTGAACTTTGACTCAGAAAC
CTCAGTGTGAGAACCTTTGACCTAGGAACCACCTGTAGTGGTTAACTGCA
ATTTGCACCCCTTAGTTTCAGGGCTTTACAACACCGGGGGCGGGGAGGGGA
AAGGCATANANCTGATGACCTAAAGGAAACCCATTGCAGCAACGCTTTTG
TGTTAAGTGTACAAATAAGTGTGTTTGTAGTAAATCCTCCAGGTAATGCCTT
TGTTATTTAATGTGTCTGAGACAATTCTGCACATTAAAGAATATAAAATA
TTACCTTGTAATCCAATTTGAAATGTGTAATTGACATTAGACTTCTATT
TGAATTTGAAATGTCTAAACAATGTGGTTAAGTTTGTAAGGTGTGTG
AATTTTGAGTCTGATTTACTACATTTTTTTTTTAATTTCTTTTTTTTGG
AGTTTTAGGGATTGCTTAGATGGCTAGAAAGATTTTATTCATCAGATTTT

FIG. 3 (1 of 52)

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TAAGTCTGCCTTGGCAGGCACTTGCAG. . .TTTGAAAGAATCAGATATATC
AAATTTGTAGTTTAAATATTTAAGGGAACCTCAATTAACCTATGCTAGAAA
AGAGAATTAAGTATTTAGGAGGATTTAATATGGTGTGAAAGTTGTGAAAA
TCAAAATGGAGACACTAATGTTAAGAAAACCTGATAAATGGAACCAGGG
AAAGGCATGAAGATAGAGTTCTCACACTTGTATCCCTGATCATGAAAAAG
ATCTGC

>Contig5

GGGTTTTTCCGCGTTTTTACCCGAAATCTTCAAGGGATGGGAAAAAGAAA
ATTGCTAAAAAATCTCGGTTTTTTGGTTTTTAACAGATATTTACACCNTGG
ATCCCATTTATTATGTTGTCCCCAAGGTTTTTCGGTGGGTTCCTAATCAGT
TAGCCCCCTCCACAGTGAAAGCACTTTACTTTATCACCTTCACCTAAAG
CATAAAATCCAGCTCTTGAAAGCTGCTCCTTGTTAACTGAATATATCCAC
ATCCCAAAGTAATGATCCATGCTTCATAATCTGCCACGGATGGATGGAT
GGATGGATGGATGGATGGATGGATGGATGAATGGATGGATTGATTTCTTG
GAGGATTTGTTGAATTTGGGAAATTCACGCCAGGACAGCTGGCCCAAAC
TGCCCGCGACAATCTGCTCGGTACAAGGGGAGGGTCCTGGAGAGGGTGCG
GCCCCGAGCCCCAGTTTGGAAATGCCAACTTGCTCTGCAGCCGGGCCTTA
GCCACTTGGGTCTGGCGTCCCTCCATTATTAGCGCCATGCCGGCTCGGGG
TGCTGCCAAGTCCCTGAGAGCACAAGCC

>Contig6

CGCGCTCAAGAAAAGCTGAAGTGTGAATGTTCTGTCTACCTTCACAGTAA
ATGCTAAGAGAATGACCCAAGAGCAGAGGGTATCACTCTGCTACGGAGGA
TTGATTGTAAGTGGCTCTCCTGCCTTAGCAAGAAATGCCAGAACCATGGT
CATTCAAGTTCTTGACCAAAAACCTGCCTTCATGAGAATCAACTTCCCAA
GAAAAAAAAGCAGAAACAGGCAAAGCTTCCAGCATGGTAGGTAATACTG
ACCCTTCTTCCCTCCTTCTTGGAGATTACACAGTAATAATGCATAAA
GCTTTGCCAATGGACTAAGCACTGCCCAGGGGTTTTTGTCTATGCCTGGAC
TGAAATGCTCTTTTTTGCCTTATCATAGAATCCAGTGCAGTCTGAGTAGA
CTCTAAGCAAAAGGGACATTTTTTCAAAAAGGCTTTAAATTGCTAGTACAA
AGAAGGCAACAAAACCTTGCCTAAGTGTGGACAGATTAACCTCACTTGGTGT
TTTGGCTCTTCAGTTTTCCCTTGGCTGCGAAGTACTCCTGAAGCTTTCTC
TGCGGCTCTTCTGCAAGCAGGCAAGCAAAAAACGACTGAACTTTATTT
CGAGAT

>Contig7

GAAGAGCCGCTAACTTGCTGTAGTGATAAGGAATGAACTAAGGCTAGGGA
CATATTAACATCCGCTGGTGGTGACTCTTTAGCCTAGATCTTACCCCACT
CCTGCTCCTTCCATATGGTTCGGTCTCAGGCTCACTACCGATCAATGGCG
TACTAAAAGCACTAACTATAGACTCCAACACGTCTGTCTGTGTTTCACG
ACAAGCCGTGGAGTTAATCCCTCTGACAGTAGCTCAGATAAGGATGGGCT
ATCATGGGCCCCGGAAGTGGGGCATGACGCTCGTCACCAACGCATGAGCTC
CCCAAGTATGCTATACCTGTCCCTATGAAGGGCTTCCAACCTCTATGTGCA
GTCCCCATGTGGAGAGTCAGGTATTGATTGATCAAGCCAGGGGTGTGGTG
AATGGGGAGCTTCCTACAGGGGTAATGATAATTGAAATGCACGGTGATGG
GGATTTTCATATTGGTCTCCTAAGGAGATAACAGATTGGATGCGGGGTCG
ATATTCCACTGCCCAGGGTGTGTACCGAGGGTATCTGCAGGTGGATCTCC
TCCCCACGTTTGATTAATACTCCTGTCTTGGGAAGCATAGACGGGCGGGG
GAAATGATGAAGGGTGACCACTCCCC

>Contig8

GGGAACGCAGTGCTCTGTACGATGGCCTTGATTGCCAATTCCTGCAGGGG
GGG

>Contig9

GGCAAGAGATTTAATATTTCATTCCATCTTCATTTGGAAGATGAAAAATTG
GGGACCAGAGAGGGGAGGGGACTGGGCCAAGTTTTCAAAGAAAAGTCAGT
AGGAATTGTGAATTCCTGGGGGCCGGGGCCATTAGTGCTGTTTTGGATC
AGTAAATGGAGATGTGAGTTTCAACAGTAACAGGGACATTTTAAATTA
AATGATTTAACCTTTAGAAAATGTCCTATTTTGTAATAATGATGGATTCA
CAGGAAGGTACAAAGAAATGTCCAGAGAGTTCNTGAGCCCCCTTCAGCCA
GCTTCTTCCAATGTTAACATCTTGCATTATTATAGTACAACATCAAACT
GGGAAATCGATATTGGTACTGTCCAGATAGCTTACTCAGATTTTGCCAGT
TATACTTCCACTCATTTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTG

FGTGTGTAGCTCTATGCAATTTTATG1...GTAGCTTCATGTAA@CACCA
AATCACAATACTTAACCTATGCCCTCATCACAAGACTCTCTCTTGCTATGC
TTTACAGCTGTATCCTCTTCATCTCCAAACCCTAAGCCCACCTCACCGCC
TCCACCATCTCTAATCCCTGGCAACCACTATTCTGTGCTCCATCTCTGTA
ATTAATTGTGTTAATTAATGTTATACAAATGGAATCATGAAGTATGTGTC
CTTTGAGATTGGGCTGTTAATTTTTCACTCAGCACAATTTCCGTGAGTCT
AATCCAACCTTGTGTGTAGCAGTAATTCTTTCCTTATTATTGCTGAATAAT
ATGCCATGGTATGGATGTATCACAGTGTGTCTAATCCTTTGCCCATTGAA
AGGAATTTGGATAATTTCCAGGTTTTGGCTATTATGAATAAAGTGAACAT
AAGACATGTGTGTACAAATTTTGGTGTGATCAAAAGTCTCATTTCTCTGG
GATAAATGCCCGGTAATGAAATGGCTGGGTTGTGTGGG

>Contig10

GCAAGAACACAGGCGCGTATTATAACCTTACTACCAAGACCTGAACCCAT
ATAAAGGTTTTATGCGTAACAATCATCATCCCTGTTCCAGAAGATTACACG
TACGACCACGCCTGGCTCACCAGCTCAGTGGGCCAGTACCAGAAATTCT
CCCAAACAAACAGTCGTGTCTGAAAACAATCGCGGTGACCTCCACGGTTA
GAAAAGCCTGTTTTCAAGTCCTGGAATTGCCACATATTAGCTGGGTAACT
TTGGGCATCACATTTACTCTCTCCGAATTTGAGATTGCAAAAACCTCATTG
GATTGTTTTGTGGATTGAAAGAAATAATGTAAATTTAGGCCGAGTGCTTT
GACTTACGCCTGTAATCCTATCACTTTGGGAGGCCAAAGCAGGAGGGTCA
CTTGAGCTCAGGAATTTGAGACCACCTCTGGCAACATAGTGAGATCCTGT
CTCTACAAAAAATTTTTTTTAAATTATCCAGCATGGTGGTACACGCCTGT
ATTCCCAGCTACTCAGGAGACTGAGGTGTGAGGATTGCTAGAACCTGGGA
GATCAAGTCAACAGTGAGCCGTGGTTGTGCCACTGCCCTCCAACCTCAGT
GACAGAGGAAGACCCTGTCTCAAAAAAAAAAAAAAAAAAGTAGTAAGTTTAA
AGAAGTTAGTGTAGGCCTGGCATATAAATGATATTGTTGATGTTGATGTT
AGCTTGAAGGCACATTTATAGGAGTAGGGATTTTATAACATTATGAGCCT
GAGAGCACATATAATGTTCCC

>Contig11

GGTCTAACATGCTCCAACCTGAAGAAACCCACACTTGTCCGGCAAGGAAA
CTACTACAGATTTCTTGACCTACTGTGCAATTCGGGGCATGCGACGGGAC
TGTGTTTTCTGGGTACGCTGTCTCAGGTTCTGTCTGGGATGTAAGAATTCAA
CTTCAGTAGTTCTCTCATAGACGCCGACGAGAGGGGCGTCTTTTTCTCT
GATGAATCTGCCAGATCTTCCACTTCATAGAGTCTAAATCCTCCGATTCTG
ATCTACTGGAGACCCCCACGTTACAAAACGTCTAACGTCGGTGACAGCT
CCCCACATAGGGAAAGATCACCTGAGTCTCACTACCTCACATTAGTGCTA
TCTCCAGCCCCATGCTATCTACGAGATGGTCACGCGAGGTTTAAGGGGTC
TCCGATTCCGGTGGTCCGATTCAGCTAATCGTGGCCCTACGTGAACGATC
ACTCCTGCTCGTAACATCGATACAGGGTCGCGCTGACAAATGGTACTACG
TAGGTTCTCAGGTCAATGCCGCGTCACGAATGAGCCTAACTACCCATAA
GTGCACGTACTGTGTTACCTTTCTGTTCTGGCCAAACCTGCTACTGTATG
CTGTGCTTGTTT

>Contig12

AGGCTCCATGTGCTCTAGCCTGATTATCTTTTCAAGTGTTTTATTGCTA
ATCTATAAGGCCCTTTCTGTAATAATGTTCACTCATTTTCTAATTAGATAT
TTTTTTTAAATGTTGAGTTTTGAGAGTTCTTTAGATATTTTAGATACAAGT
CCATTGTCAAATATGTGATTTACAAATATTTTCTCTCAATCTGTAATTTA
GTTTTTCATCCTCTTAACAGGGTCTTTTGGAGAGCAAATAATTTGATTTTC
ATAAGGTTCAAATTATTAATTTTTTCTTGATAGTTCACTTCTAGTGT
TAAGTCTAAAACTGTGCCTTGTCATAGGTACCAAAGGTTTTCTCCAGTT
TTTTTTCTAGAAGTTTAGAGTTTCATGTTTTACATTGGAGTCCATGATCC
ATTGTTAATTAATTTTGTATATAGGTAGATGTTTAGGTTTAGGGTTTTT
TTAAAAAAAATTACATATGTTTAATTGCTCCAGTTCCCTTTTATTGAAA
AGGGTATCCTTCCCTCCATTGAATTGCCTTTGTCAGAAATTAATTGGACAT
ATTTGTGTGAGTCTATTTCTGGGCTCTTTATCATGTTACTTTTAAAAAAT
GCATCAGTTCTCCACCAATACCTCATTGTCTTGATTATTGCAGTTATAT
AGTAAGCCTTAGCATTAGGAAAAGTGTTTTTCTGCTTTATTCTTTNTCA
AAAAATTTTTGGATATTCTAGGGCCTTTACATATAAATTTTAAATAACT
TTGTCTATGTCTAACCGAAAGCCTTATGAAGATTTTGATAAGAATTGCAT
TATGCCTATACATTAATTTAAAAAGAACTGATGTCTTTATTAGTTGATT

CTGCTAATCTATGAACA1AGCATCTCT...CAAAGCATTTAGTCTTTCTT.
AATTTCTGTCATTAATTTTTTAAATTTTCATCCTAAAGATTCTGTATAT
GTTTTGTTGAATTTATGCTTAAGCATTTCACCTTTCTTGGTAACAATTATA
AATGATTTTGTGTTTTTTATTCCACTAGTTCATTTTCAGTGTGTAGAAAA
GCAATGAATTTTGTGTGTTGATCTTTGTTCCCTACATCTTGCAACATTAT
TGAACCTCATTTATTAGTTCTAGGAGGTTTTTTTCATTTTTCTTGTAGATAC
CTTGAGATTTTCTATATAGACAGTCATGTTGTCTGCAAACAGGCACAGTT
TTATTTCTTCCTTTTCAATCTATATGCCTTTTTTTTTTTTTTGCCTTAT
TGCAGTGGCTAGAACTTCTAGCACTATGTCAAATAGCATTGGTGAAAGCA
GACATCCTTGTTCCCTTGCTTAGAGGAACATTTGGTCTTTAATCTTGGAT
TGCG

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GCGCCTCCTTTTCTCTTCCAAAATTTCTCTTGTCTAGTTATTTGTCCAGG
GAAATTTGAAAGCTCACTTACTGTGCAAGTCAGCAGGAAACAACCTGGGTC
TGTGCACAGCACCTAGCAAAGTTCTGCTCTAGGAATTACACTTTGGCCCT
GAGGTAGATTTCTACAAGAACCTTACCTTCTAAGCAGCACTGGGGTTCAT
CTTTTTCCCAGTCCTCAGAGCCCATTTTCACTCCTGAGTTCTCCCCACA
AAGGACATTTTCAACGTTGAGTTTATTACTCAACAGAAAATGGAATGAAG
TCCAAGACCTAAGGAGATAGAAAGGGGACCAGTTATGGCATCTTCTCACC
CCAGGACACCTTGCTGCATGTCTCTAGTGCTGAACAGACCACTGGCCTTG
CTCTGTAGTTTGAAATGCTCGCTGCAACCAGAAAGGCACCAAGGGGCCAG
ACCATGCTCTCCTGTCTATCACGCCTTCAAAGCAGAAATTTCCCAAACCTT
GAGTCACAGTGCTAACACACGGGGTGCCATAACATTTTTGTTGATTTTGG
CATTTTACAAAATAAAAATAAAAAGTTAAAAATGCATTGCTCTATTCTT
GGGGCTGGCACACTATTGCCTTTGGCCAAATCCGGTCCCTGACTGTTTTT
TTAAATAAAGTTTTATTGAAACACAACCATGCTCTTGTGTACATATTGTC
TCTTGGCTGCTTCGAAGCTACAATA

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GTGTTGCTTTTTTAACACTTACCTAAAATTACTCTGTAATCCATGGATCC
TTAATTTATTTAAAAAACTAATGTTAATGAGTAGCTTTATTTTCTCCCA
TCTAATTTAAGGCCACAGAACACCTTCACTTACCTCAATCCTCTCCCA
CTTACATGCTTTTAATGTCATATATGTTAATACCGTATACTTTTAAACT
TTCTAAAATAGCATTATTTTATAGCATGAGTGTTCAATTACATTTTGTCA
TATATTTAGAATTTTCTTTGCTCTTCGTTTCTTCTTCTATTATGACTCC
CCTCTGGGATCATTTTCTTCTACTTGAAGTACATAGTTTAGAACTGCAC
TATTCAATACAGTAGCCACTAGCCATGTGTAGCTATTGAAGTTTAAACTA
AGTAAAATTGAGTAATATTA AAAACTCAGTTCCTTCATCTCACTAGCCAC
ATTTCAAGTGCTCAGCAGCCACGTGCGACTAATGACTACTGTACATCAA
CATATAGAACATTTCCATCATGGCAAAGAGCTCTATTGATAGTGTTTCATC
CAGAGTTTCTGTTCCAGGACCAAACCTGAGGGTTGGGCTGCTATTTCTCAT
GGCCCAATAACAAGATGCAGATGAGCTGGGGAGGAAGAGAGTTTTTATTT
CTGCNACCATTTACCGGGAGAAGGCCTGGAAATCATCACCAGGCCAACTC
AAAATTATTACGTTTTTCCAGAGCTTATATACCTTCTAAGCTATATGTCTA
CGTGTAAGTGTCATTACCTGAAGACGTTAGTGATTAACCTCTTTTAAT
CTGTAACCTAAGGTCTGAGTCCGGAAGATCTTCCCCTGGAGCCTCAGTAAA
TTTACTTAATCTAAATGGGTCCAGGTGCTGGGGTAATTACCCTTATCTTG
TCCCCTGCTAAATCATGGAGGTTTGGGGATTCTTTTAGAGCACCAATAAA
CTTGTTTGTGGAGGCCTGGGGGTTTCTTCTGACCCACAATAAACTTGTT
TAATCCTAAATGGGTCTGTTAAGAATTCCTTCTTTATTTTGTTCATATT
TAAGGCCAGAAAAGGCCTGGGCAAACTCTTGATGGGCTTTTGTACAT
TCCAGCCTTTGTATAAGAACACTGGTTTTTAATATTTAACTTAACCATTT
AGTCAGTACTGAAACAGTTGTTATAGAGATCTGCATTAGTGAGACCTGGC
CTGCCACATTTCTTTTCTGAAGATCTTATGGTAGTGATCACCTTTGTGA
AAGGAAAATAAATCTTGGGACCTCAAATCACTAAGCCAAAGAAAAAGT
CAAGCTGGGAAGAATCTGACACTTAAATCCAACACTGCTAACTCATTCAT
CTCACTCATTCATTCTTTTATTTTCTTTTTTCTTTCTTTTTTTTTTTT
TTTTTTGAAACGAAGTCTTGCTCTGTCAACCAAGCTGGAGTGCAGTGGAT
CTCAGGTCACTGCAACCTCCACCTCCCGGGTTCAAGCGATTCTCCTACCT
CAGACTCCTGAGTAGCTGGAATTACAGGCACCTGCCACCACGCCTGGCTA
ATTTTTATATTTTATAGTAGAGACGGGGTTTCACCATGTTTCATCAGGCTGG

FIG. 3 (4 of 52)

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TCTCGAACTCCTGACCTCGTGATCCGC...CCCCCTCGGCCTTGTTTGCT
GAGGTACTGTCTAAATGCTGGAAGTGAAGTGGCAAGCAAGACATCCCTA
CCCTTGAGGAACTGTAATCTAGTCGGAAATACAGATGTCAACCAAGTCT
CACACAAGANATTGTACAAAACCCCTAGGA

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GGAAAAACCTATCACCGCCTCCTATGGAAGTTAAACAAAAAGAAAAGTA
ACAAAGGAAATGAATATTTTATTCTGGAAGAACATTGAAAAAGAACAGGA
AGAAAGAGAAAGCACAACCTCGAACTGTCCACTAGAATTGACAACACTCTGA
CAGAATGTCTGAACCTCATCGAAGGGGTAAGTGAAAAAATAAGCTCCTC
CAGCTTTGGCCCAAAGTCTTATAATTTTTTAAACATATTCCTAAATATAAT
ATAGGAGAGATAGCCTTCATCTAAGTAGAAATTTAGCTACTCTTGTAAT
ACAGAGTAATAATAATAATGACATGCCATAAACAGTGTCTTTTGTGTAT
CTGTGCTTTTATAAGCACTTAGCTAAGATTATCTCACATAATTATCATAA
CCACTGTTACTATGACCACCTTTACAAACAAAACCTGAGGCACAAAGAAGTT
GGAAACTAATCCAAACAAACTGGCTCCAAAAGGAAGTTTGCTTTCTTTG
GGTATCAAGTTCTGAAGAGTACACATTTAACATTGAACTGAGGTCAGAA
GGCAAGTTTCTATGTAAAGTTGGAGTATTCTGAATACTCTGGGTAGCTAC
AAATAGTATTTAAATTTTATCTTGGAATTCTGCAGATAAGGATAAAATAGA
TGGTAGGCAAAGAGTATGATCCTTAGGAGAAATTTTCTGAAGGAAAAA
TATATTAATAAAAAATGATGGAATAAACTTCTAAGATCCTTGCCTAGAGC
AAAACCTCATTCAAGTCTTTGGCTGGTAATGTTGAACATCAACAAAAAAA
GGAAAAGTTCAGTTTAAAGTCTACTCCAGGCAACATTTTCAACATCCAG
TTAAATATTAACATTTTCTCTTTGTGGAATTGAACTAGAGTTCTTTTCT
TATCCTCTTTTGGTTGTTGTATTATTTAAAAATGAGTACCTTTTATT
ATTGAAATCATTTCAGTAATGCAGATAAATGATCAGCCCTCTCCCTGTA
CAAACATACATACTTAGGCATCCCAAACCTTCTCTCTGGAGGTGACCACCA
TTGCCAGTCATTCTATTCTGTTTTTATGATGTCATGTCATACAGTATAGGTATG
TCGAGAAATGAAGTATTATATTTTGTGAGTTGCAATTCTTTTATTACCA
TTTTTGTGTACTTTGGTTGTCTTTTCTTGTTGTTTCTTAGTACCAATGTT
ATGCTGACTTAGGCAGATGAGTTGAGTATTTTCTTTTGGCCCTATAAAC
TGAAATAGTTTGTATGACATGAGAATTATTTTATTTTGAAGGTTTG
ATAAAAACCTTGCCCATAAAAATCGTCTGGACCGGTTTCTTGAGGATGCCT
GTGTTAGAGCC

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CGCTTTAACCTGGGCTACCAATGGTTCGTCAAGTTCTAGATTCTCTATTA
ATACCTTTTTCTTGTTCTTTCTCTGGTCTGTTTTTCAAGCCCGAGTCTCT
TAGATCTGTCTCTAATATTCCTATTGACTTTACTTCATTTTCTAAGTCT
TTATCCTTTTGCTTTACTTTCCGAGAGACCTGCTTAACCTTATCTCCAA
CTCTTTTATTGAATTTCAATTTCTTTTACTATATATTTTACTTTGAATA
CACCTCTCTCTTCTCACATTTTCCCCCATAGTATTTTGTCTTCAATTGA
CAGTTCTACTATCTTATTACTCTGGAGATATTAATAATAGTTTTTAAAT
TTTATTTATTTTATTTTCAAAACAGTGTCTTACTCTGTCACTCACGCTG
GAGTGCAGTGGTGTGATCATGGATCACTGCAGCCTTGATCTCTGAGCTCA
AGCTATCCTCCTGCTTCAGCCTCCCAAGTAGCTGGAACCAAGGCATGTG
TCACCATAACCAGCTAATTTTTTTTGTGTTTGGAGGTGGAGTCTCACTCTGT
AGCCCGGTCTGGAGTGCAGTGGTGCAATCTGGGCTCACAGCAACCTCTGC
CTCCTGGGTCTGGTTCAAGCAATCTCCTGCCTCAGCCTCCTGAGTAGC
TGGGATTACAGAAACACACTACCATGCCAGCTAATTTTTTGTATTTTGT
AGAGACAGGGTTTCAACATGTTGGCCAGGCTGGTCTTGAACCTCTGACCT
TGTGATCTGCCCACCTTGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAG
CCACTGCACCCGGCCACTAATTTTTTAAATTGTTAATAAAGACGAGGTCTT
GCTATGTTGCCAGTATGGTCTTGAACCTCTGGGCTTAAGTAATCCTCCT
GCCTCAGCCTCCCAAAGTGTGTTGGGATTACAGGTGTGAGCCACTGAATCTG
ACATTTTTTAAAGTTTTCTTCTCTTTACCAAGTCTTTTTTCCCCTTTCT
GCTTTTTTGGGTTGTTTTATTTTGTATCTCTATCTTGCTAGAACTTTCTG
CAGACGTTTAGTAATACTAGATTTTTTGAAGTGGGCAACTGGAAAGCTGA
TTGGAACTCTGAATACATGGGTGAGGCTTGTGGCTGTGAGTGTGATTG
CTTGATGTCCTGGCAAGGCCAATGGGTTTGGGACCCCTACTATTAGTATA
GGCCTGATTCCCTGGGAAAGGCTCTTTTGATCTCCTGCCTGGAGGATAAA
GGCCTGGCTACCAGCCTTCTGTGTGTAATGTGAGGGAGAAGGGCTGGAGT

FIG. 3 (5 of 52)

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ATTCAACATCATGCTGAA.CCTTTCAA.JATCATCTTGTTTTTAGTAATC
TCCTACCTTAACCTCTCTGTCTTCTGCTAGTATGGGAAAGATGACCTGAAA
ATCTAACCATTTATTTTTTCCCCCATTAATATCATTTTTATGATTATTCAGA
AGTTAAATAATTGTCATGCTGTCCTCCAAAAAGACTGAATCAACTAGCAA
CAAATAAGAATTTTCTCACAGCTCTGCCAGCATTTTAAAAGAATAGCTTT
ATTGAGCCCAGGAGGTCAAGGCTGCAGTGAGCTGTGATTACACCACTCTA
CCCCAGCCTGGGTGACAGAGCAAACCCTGTCTCAAAAAAGAAATTTAAG
GAACAGCTTTTATTGTTGTAAAATAGACATACAATAAACAGAGCACATATT
TAAATTGTGCAACTTATACTTTGATATAACCCTGTGAAAACATCACCACA
ATCAAGATAGTGAATATATTTATCACCTCCTGATACAGTTTAGCTCTGTG
TCCCCACCTAAGTCTCATGTTGAATTGTAATCCCCAATGCTGGGGGAGGG
GCTTTGTGGGAGGTGATTGAATTGTGGGGGTGCACTTCCCCCTTGCTGTT
CTTGAGATAGTGAATGAGCTCTCATGAGCTCCCCCTTCACTCACTCTCTTT
CCTGCTGCCATGTGAGGATGTGCTTGCCCTCTTCTTTGCCCTTCTGCCATG
ATGTGTTTCCTGAGTCCTCCCTAACCATGCCTCCTGTACAGCTTGCAGAA
CTGTGAGTCAGTTAAATCTCTTTTCTTCATAAATTACCCAGTCTCAGGTG
GCTCTTTATAGCAGTGTGAAAAGGAATAATATACCTCCTAAGTTACCTC
AAGCTTGTTTTTAATTCTCTCTCCTCCCTTCCTTCATTGCCAAGCAAACA
ACCACCTGTTTTCTGTCACTATAGATTAGTTTACATTTTGTGGGTTTTTT
TTTTTTTTTGAGACAAGGTCTGACTCTGTTGCACAGGAGCAGAGCAGCGTA
TC

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CGCGTTATAGGAGATGCGAACTTAAGAAATGATGATAAGGAGACTTTATT
AAATATAATTTTGAATTATTTTGCCATTACAGAAATTCTAATTATTTAAA
ATTCTATTCATAATTTTAAATCACTGTACTTCCCAAGCTTAGCTTAGAAT
CCTTCTGTGCTGAGGATTAATTTTAAATTTGTCTTTTATAGGCCTTATCTA
AAATCCAAGAATAATTGCCAGAATCAACCACCTTCTAAATCTGTAAGTAG
AAATTAGTCTTTTTTAAAAATATGCATTCATAAGTATGATTAGTAATAAAA
ATAATAAAGATGTTAGCAACCTAAAGAACATGTATTTGAAAGGTATTTCT
TACAGATATAAAAAACAGTTTGGTTTAAATAAGAGACAATCATTTTTTGAAA
AGTATGACATTTTTTTGAAAAGTAGTTTAGTTTTATTAACCAAGAAAAGCC
TCAAGTGAACCTTAGTCCTCTTGATAGCTAACATTTATTGAATGCTTACT
GTGTGCCTGATACTTTTCTGACTTGCATTACCTCACTGAGTCCTCACAAT
CTTATGAGGCTACTATTAGTAGCCCCACTTTACAGATGAGCAAACCTAAGT
CACAGAAAGGTAAATAGGTCGTATAGCTATTAAGTGACAAAGCTGAGAG
CCTGTGATCTTAACCACTTTGGTATGCTGCCATGAAGTTAAATAGCTCAG
TAGTCATTAAAAGAGAACATTTGCATTGAACCTTCCAAGCCACTTAACAA
GSTATATGCTTCCTAATCAATTTAATTTAGCTACATTAGATAGAATGGTAA
AGGATCCTTAACTTAAAGTTTAAATGGAAGAAATTAGCCCTCTGAAAGAG
GCACAGATTATTCATCTGCAATAAAAAATCTCACCTTTAGTTTTTTTAAAC
ATAGTTTTTTATCTGTGTTCTGAAATGTAACCTAAACAGTGCTTCCTGAAG
TGAAAAATTCTCACTGGTGAGAATTTTAATAAGTTTTAATGATTCACCAA
ATCACTTCAGTCATATTTAGTCATATGCATATGCATATATAGACATATA
AGTTTTTATCTGTGTTCTGAAATGTAACCTAAATAGTGCTTCCTGAAGTG
AAAAATTCTCACTGGTGAGAATTTTAAATAAGTTTTAATGATTCACCAAAT
CACTTCAGTCATATTTAGTCATATGCATATGCATATGTAGACATATATA
TGTTGTATGTATACATGACATCATTAGACACTGTGAAGGATAGCAAAATG
TATATAAGGCAAAATTTATGAACAATGGTTTAAACGTTTGGGAAGCACTGG
GTTACACTTTTACTTTATGCAGATTGAACCAGTATAGTATGCAAGTCTTA
AGGAAAAATCTACTGGAAAGGGCCCTCATTACAGACTTCCCAGAGGCTTCT
CTGGAAGTTGACAATACTGACTTCAGTACATCAGCTCGTAAATGAGGATG
ATACCTACCTTATCTGCTTTACACAGTTGTAAAAGTAAAAAGTGAACCTCA
GGAAGGGAATTACAGAATTTAGGAGAACTAAAAGCACGATGTAAATAAT
AGTCATCATTACAGTTATATAATGCTTGACAATTTATATAACACTTTTGA
TACATGACAACAATAACTAACCCAGACATGTTTATATAACATTACCTCA
CTCAGAACAACCATGTGAGGAAGTTGGCCATATGCTTTAATGTCCAAACC
AGGACACTTTTGAGAGTAAAAAGCAGTACTCTTTGACCAACAGGCATAAA
TCAAACTATCTTGTGAAAACCGGGATATATGGCATCCTTCCTAGATAAT
AGATACTTTTACTATTATTAATTTTGCTGTGAATCTAAACCTGCTCTAAA
AAAGTTAATTTTAAAAAGTAATGAAGTACTGATACATGCTACAACATGGG

TAAATCTTGAAAACGTTAAGCTAAGTG...AGAAGCCAGACAGAAAAGG...
ACATATTACATGATTCCATTTATATGACACATCTAAAATAGGCACATCTA
TAGACATACAGAGACAGAAAGTAGACTAGCGGTTGCCAAGAACTGCAGGG
AGCAGAAGATGGGGAGTGA CTGCCAATANGAAAACGCATTACGT

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TGAATCGCAATGATATGTGCCACTTTGCACTCTCTGTGACATATATAATT
ATTTTAAATGCATTCATTTTTTTCTCAGAGTGCATTCGTTTGAAAACATA
GACGGGAAATACTGGTAGTCTTCCTTGTCAGTTAGAAACACCCAAACAAT
GAAAAATGAAAAAGTTGCACAAATAGTCTCTAAAAACAATGAACTATTG
CCTGAGGAATTGAAGTTTAAAAAGAAGCACATAAGCAACAACAAGGATAA
TCCTAGAAAACCAGTTCTGCTGACTGGGTGATTTCACTTCTCTTTGCTTC
CTCATCTGGATTGGCATATTCCTAATATCCCCTCCAGAACTATTTTCCCT
GTTTGTACTAACTGTGTATATCATCTGTGTTTGTACATAGACATTAATC
TGCACTTGTGATCATGGTTTTAGAAATCATCAAGCCTAGGTCAGCACCTT
TTAGCTTCCTGAGCAATGTGAAATACAACCTTTATGAGGATCATCAAATAC
GAATTCATCCTGAATGACGCCCTCAATCAAAGTATAATTTCGAGCCAATGA
TCAGTACCTCACGGCTGCTGCATTACATAATCTGGATGAAGCAGGTACAT
TAAATGGCACCAGACATTTCTGTCATCCTCCCCTCCTTTCACTTACTTA
TTTATTTATTTCAATCTTTCTGCTTGCAAAAACATACCTCTTCAGAGTT
CTGGGTTGCACAATTCTTCCAGAATAGCTTGAAACACAGCACCCCCATAA
AAATCCCAAGCCAGGGCAGAAGGTTCAACTAAATCTGGAAGTTCCACAAG
AGAGAAGTTTCTATCTTTGAGAGTAAAGGGTTGTGCACAAAGCTAGCTG
ATGTACTACCTCTTTGGTTCTTTTCAGACATTCTTACCCTCAATTTTAAAA
CTGAGGAACTGTCAGACATATTAAATGATTTACTCAGATTTACCCAGAA
GCCAATGAAGAACAATCACTCTCCTTTAAAAAGTCTGTTGATCAAACCTCA
CAAGTAACACCAAACCAGGAAGATCTTTATTATCTCTGATAACATATTTG
TGAGGCAAAACCTCCAATAAGCTACAAATATGGCTTAAAGGATGAAGTTT
AGTGTCCAAAAACCTTTTATCACACACATCCAATTTTCATGGCGGACATGT
TTTAGTTTCAACAGTATACATATTTTCAAAGGTCCAGAGAGGCAATTTTG
CAATAACAAGCAAGACTTTTTCTGATTGGATGCACTTCAGCTAACATGC
TTTCAACTCTACATTTACAAATTATTTTGTGTTCTATTTTCTACTTAAT
ATTATTTCTGCAATTTTCCCAATATTGACATCGTGTATGTATTTGCCATT
TTTAATATCACTAGACAATTCAATCAGGTTGCTACGTTGGTCCCTTGGGT
TTACTCTAAATAGCTTGATTGCAAATATCTTTGTATATATTATTGTTTTT
TCTCCTATCTTGTAATTTCTTTGAGCACATCCCAAAGAGGAATGCCTAGA
TCAATGGGCACAAATAATTTGACAGCTCTTATTAAACATTATTCTGTAAG
TAAAAACTGAACTACTTTTCAGTATCACTAGCAACATATGAGTGTATCAG
CTTCCTAAACCCCTCCATGTTAGGTCATTATGAACTTATGATCTAACAAA
TTACAGGGTCTTATCCCACTAATGAAATTATAAGAGATTCAACACTTATT
CAGCCCCGAAGGATTCATTCAACGTAGAAAATTCTAAGAACATTAACCAA
GTATTTACCTGCCTAGTGAGTGTGGAAGACATTGTGAAGGACACAAAGAT
GTATAGAATTCCATTCCCTGACTTCCAGGTATTTACACCATAGGTGGGGAC
CTAACTAC
CATGCACACACAATCTACATCAACACTTGATTTTATACAAATACAATGAA
TTTACTTTCTTTTTGGTTCTTCTCTTCACCAGTGAAATTTGACATGGGTG
CTTATAAGTCATCAAAGGATGATGCTAAAATTACCGTGATTCTAAGAATC
TCAAAAACCTCAATTGTTTGTGACTGCGCAAGAAGAAAACCACCCATGCTG
CTGAAAGTCAGTTGTCCTTTGTCTCCAACCTTACTTCTTTACCTCTCAT
ATGTTTGTGAATAAGCCCAATAAGCAGACNCCTCCTACAAAGTGAACCTG
GTCTCTTTCCTCCTAACAGGG

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GTCTTGTAACACAGGTAAGACGAGTTCAAGTTTTATTTCTTGNTTTTAGA
ACGGTAGTGAGCGGTTTTTCAGCNTGAGACCACACCTAAGGTAAGTAGCTG
AATTGGGGTTTTGTCTTGGCTAAAGTTTAAACAACCAGCTGGTCTTAATTT
CTCCTTACCATTAGAGCACTCAGTAATCATATAAGTTGTGTGATCATTCA
TTTTGCTTAACTGTTTGTCTTCTGTTTTTATTGCTGTTTCAGTCTTTTTCC
CATTGGGTTTGACCTACTCTATCTGACTTGATCAAATCCAAAGGAAATTT
CCAAATTATGGGGAATGAGGCCTCTGAAGTGGCTAAATTCCCACCCCTCCC
ACACACACAAACGTGGTATGGTGGGGGAAAAAACGGCCAGCAAAAGAAAA
AAAAAAAGGAAAAGATGTTTCAATTTGACCACCAACGGGCTTTATTTAC

FIG. 3 (7 of 52)

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ATAACAAGGCCACCTTT...GCTAGCCA...CCATACTGAAAGAGCAATG...
TGTTGCCCCATGCTGTGGGTTCCATAGCTAACGTTCTGCCTTTTTTCCTA
CCACGACAGCCTGGGTTTGGTTCCTAAATCAAGCCTTTTCTGGTTTGATA
CTTGGTAATGCTGAAATAGCAGCAATTTGTCCTAGCTGAAATATCGTAAT
AAGATTTTAAAAGATTTATTTTAAAGGACCTCAATAGTTAAAAGTCAGCT
TAATTAAAAGCTAACATCCAAGATGTGTGCATGTGTATGTATGCGTCTTT
GTATTTAAATAGCCCTCATGTTTTTTTTTTTCTTTTCTTAGGAACCTTGCCTT
TTTTTGAGCAAAAGTTTTTTTTTCTTCTCTGTGACTGGATTCTGTTTTCTT
CATTTACTTCTGCTGTCTCTCTTTTCTCTTGCACCGTCTGCTGCATGAGA
GCCCTAAAATAGTTTATAATAGCCTGGGGTTCCTTAAAGAAAATGGAGAA
GGTGCCAGGCTCCCTTTTAGGGAGAACTTCTATTTTTCTTATGGAATC
CCTAGAGTGTAACAGACAAGTTCATTTTCACTCTTAAACTGCTTGCCTT
TGTGTTGTGTTACCTGATTTTTTTTACTATTATTTTTTACTAGCTATT
GCAACAGAAGCTACTCTTGGGTTTTCAAGGAAGATTGTAGTTTAGACATG
TAGAAATGTCTTTTAAAAAAAACAACTTTTTTTTAAAGTGCACTGTAA
AAGCATCATATGGTCTAGCCTCCTAATAATTTTCCCTTTTTTGGAGACCAG
GATTCAGGGTGGGCTCTGCCAGAGCTCAGAGATCCAGTTAAAAGAGAGG
TAGTCTCGGCCGGGCGTAGAGGCCAGCCTGTAATCCCAGCACTTTGGGA
GGCCGAGGCGGGCGGATCACGAGGTCAGGAGATCGAGACCATCCTGGCCA
ACATGGTGAAACCCCGTCTCTACTAAAAATACAAAATTAGCTGGGTGTG
GTGGCAGGTGCCTGTAGTCCCAGCCACTCGGGAGACTGAGGAAAGAGGAG
AATCGTTTGAACCCGGGAGGCGGAGCTTGCAGTGAGACGAGATGGCGCCA
CTGCACTCCAGCCTGGCGACAGTGAGACTCCGTCTCAAAAAAAAAAAGAT
AGGTAGACTCGATGTTGTCGTACCCGAGCAAGTTAGAGCAACGCCACACT
TTGAGACGAATTTAAGAGTCCTTTATCAGCCGGCGACCAAGAGACGGCTA
ACGCTCGAAATTCTCTCGGCCCTTGAAGGGGCTTGATTTTCTTTATG
CTTTGGTTTAGGAAGGGGAGGGGAGCTCAGTTGCAACAATTCTACAGGAG
TAAAAACATGCAAAGAAATTAAAAAGACAAGTGGTTACAGGGAAACAAAC
AGTTCCAGGTGCAGGGGCTCTAAATCTATCATAAGATGTTAGGTATGGGG
GCTCTGCCGGACACAACTCAAGGCTTTATGCTGTTATCTCTTGAGCGAA
ATCCTGGGAACCTTCGTACATTGCTTGCTTCAGTACCTTATCAGTTAATCG
GACTCTTTGATATGTTGGGAGTCAGCGTACACAAGTTAACTCCTTGAGGA
AGGGGGTGGGTAAGGAGTCCTTGATGTCTGGTAAATGAAGGAGCGAAATC
GAGTTCCTCTGGCTTTCTCAGCTAAGGGAGAGCTTATTCATGTGGAAACA
AGGCTAAGTGATTAAGGGAGAAAGGGAGAGTCTGAAAACAAGGTTAGGTA
TTACAATGTCAATAAAATTGGTCTCCTTATACAGTCCTATGGTAGATTTC
TTTCCATCTTTAATCTCCCTCTAGCACCACCAGACTTTTTCTCTCTGTAC
CTTGAGATGTAAATTTTGCTATCTGAATTTTCGTCTAAGAGTTGTTTCCT
TTAATATGCAAATTTAGGGTTATTTAGCTGACAACTGCCAAAGTAGTGAA
ACAAGTTATCAAGAACTTGAACGTCTAAGGTAGGAAAAAAAAAAGTCTTT
ATGAATCTATAAGATGTACTTCTATTGGCATGCCTAATACGTCTATGTAT
TTACGTGTTGTGTACACAGTTTTTCACTACTGAAAATATATAGAGGAGTT
CTAATTAATTGACTTAAGACAATAAAAGCGCTTGAATCAAATACCTTATC
AGGAAAAAGGAAAAGACAAGTCAAATGCTTGTTCAGTCTATATAACTTA
AGTAAAATCTTTAATAAATAAGCTAGCTTTAACATTATTTGAAATGTCTT
AAGAATTGCCAGCAGGTTCTGGGTACAGAACTAGTGGGGGTGCAGTGGG
GTGAGGGTTGGTGGGGTGGGNGGTNNNACNNNNNCNCCCCCCCCCCCCC
CCCCCCCCCCCCCTCCCCCCCCCGCCCCGNGCGGGCCGCGCCCCCCCCCGC
CCCCCGGCCCCGCCCCCGCGGCCCCCCACCCCCCCCCCCCCCCCCCGC
GCCCCGCCCCCCCCCCCCCGCGCCCCCACCCCCCGCCCCCCCCCGCCCCC
CCCCCCCCCCCCCCCCCCCCCACCCCCGCCCCACACGCCCCCCCCCGAC
GCCCCGCCCCCCCCCCCCCCCCCGCAGCCGACGCCCCCCCCCGCCCCCG
CCCCGACCCCCGACCCCCCCCCCGCGCCCCGCCCCCGCCCCCCCCCG
GCCCCCCCCCCCCCGCGCGCGGCGCCCCACCCCCCCCCCCCCAGCCCCGACC
GCGCGCCCCCCCCACCCCCCCCCCAGCCCCCGCCCCCGCCCCGACCC
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GGCAGTACGCTATAATTCCCTCTTACCTTACCTCATCTGTTCTCTGATG
GATGTACTTTTTTTTTTAGTTTCTAAATTCCCTTTTCTTTGCTCTGGAG
ATGGGTGATTGATGTAGTCTGGGTATTTGTTCCCTCCAAATCTCATGTTG
AAATGTAATCCCCAGTGTTGGAGGTAGGGCCTGGTGGGAGGTGTTTGGAT

CATGGGGGCAGATCCC. ATGAATAGC .GGTACTGTCCTCTCAATAG. 3
 AATGAGTTCTCCTGAGATATGGTTGTTTAAAAGTGTGTGGCACTCCCCCA
 TTGCTCTCTTGTTACTGCTTTTCGACATGTGACATCCCTGCTCCCCTTCGC
 TCTCTGCCATGATTGAAAGTTTCCTAAGGCTTCGCCAAAAGCTGAGCAGA
 TGTGGGTGCCATGCTTGTACAGCCTGCAGAACTGTGAGCCAAAATAAACT
 TCATTTCCATATAAATTACCCAGCCTCAGATATTTCTTTATAGCAACATA
 AGAGTGGCTTAATACAGGCTGGGCATGGTGGCTCACGCCTGTAATCCCAG
 CACTGTGGGAGGCTGAGGGGGGTGGAACATGAGGTCAGGAGATTGAGACC
 ACCGGCTAACACGGTGAACTCCATCTCTACTAAAAATACAAAAATTAG
 TCGGGCGTGGTGGTGGGCGCCTGTAGTCCCAGCTACTCTGGAGGCTGAGG
 CAGGAGAATGGCATGAACCCGGGAAGCGGAGCTTGCAGTGAGCCGAGATT
 GCACCACTGCACTCCAGCCTGGGCGACAAGAGTGAACTCCATTTAAAAA
 GAAAAACAAAATTTCAAACAGAACAAAATGAAAAAATAACCAAGTGAAA
 GGCCCCCTATAAAAACCCCTCTGGGGCCCATCCTCCCACCCCTCAAGTGA
 AACCACATTTAACAATTTGGTGCATATCTTTCAAACCTTTTGTGTACA
 CATATAAAAAACATACATGCTTTGATTTGGCTCAGACTGTACATAGTGTT
 TTCCCTCTTGCAATTTTACACTTAATATATCTTTGACATCTTTCTATGTCA
 GTGCATGTTGGCTCGATGATATTCTATCATTAAATACCCCTTCCAAAATG
 GTAAAATCATTTTAAAAAATCATTCACACAAGTACATATTTACAATTTTA
 AAAGAAAACAGAATCCCAAAACACAACGACAAACCTCTAAAAATAATCTC
 TATCTTTCCACCAGCATGGAACAGTTCATTCTTTTTTACATAAAACGAA
 TTATGTGATTGGAAAGATTAACTCTAATCTACACATTTATATACAGAATG
 TTCTATTTGTTAAGCCTATCTGAAAATAAAAAATTGAGATGATTAATTCA
 CTTACACTTAGAAATTAAGTCAATATACTATGAATACACATTGTGATCAG
 TTATAATATGATGCTTCTTAGTCTAGGGTTTCAATTAAATAACAGTAAAA
 AAAATTGGATAAATAAGACAGCTAATAACTGAAAAATCCAGAAATTCAA
 GATTATATTGCCAACTAAACACTGCCATTTACATTTTTTTTTCTACTT
 GGTAGCAAATGCTAATGGAATTCAATCCTGATTACTTAAAGTCAGTTCAC
 ATCACACATTCAATCAGGATAATACGAACATAATATGCCTACTATAGCGT
 TAGATTAAGACATAAAATTTTTTTGCTTGAAAGTAATGACTGCGTACCAC
 TTGAGACATTTGTCAACCACTTCAGCACATTGTTTACGAGTGACTGGATG
 TCCACAAGGAATAAAAACGACAGCAATATTTCTATCCATACAGATTTTGC
 AAAGCTTCTCCTCTTGCAAGGTGTCTTAGCTGCTCTTCAGTACTAATCTCT
 TTCTGCAATGAAGTCTGACTTGATTGCTCTTGTTGTTACTGTCTTTCTGAGC
 CTTCACTGGATCTGCAATCAGAACCTCAAGTGATTTACAGTTGCTCCCAG
 ATGTCTGAATTTTTTCTCCTCATTATTTTCTTAATGTCTTTGAACTGAAC
 CCCATTTCATATAGCTTCTTGTAACCATAGGATTATGGAAGATGGTATCAAT
 TTTTCTAGTTAGTGATGGCGTTTTTTTCAGCAGTTCTTACCAGACACTCCT
 CAAGTGAATGGGATAAATGAATATTGTTTATATATTTTCGTGTCTTCTGT
 TCTAACAGATATTTACACCCTGGATGCCATTAACATGTTGTCCCAAGGGT
 CTTNCTGGGCT

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CTTTCTCCCTTTTTTACCCCCATTTTCGTAGGGATTGGTTAAAACCCATG
 TAAAAAATCCAAACACCGGCGGGGAACGGGGGTTCAAGCTCGTATCCCCA
 CCACTTTGGGAACCCAAGGTGGCAGGATTGTCGGAAGCCAGGCATTTGAG
 CCCACCCTTGGGAAAAAAGAGAACCCCATTTTTTTTGAACAAAAACC
 CCAACCTCCCAGGAAAGAAATAAGTATGGCTGGGTTGAAGTCACCAAAG
 ATGGCCGACTGGCTGGTCAAGTAACCTTACCTGATGGTTTCGTAGAATATT
 TACCTTCACCCAGGTGGGAGAATTGCTTGAGCCAACCTCAGTGTGGATT
 CAGGAACCTTGATTTAATTGGTATCGTGATTGTGGATTAGATTCTCAGGGA
 TGCATTCACTAAGTAAAAGTGATAATAGCTACTTTTAAGTAAAATAATGA
 ATGAATCAAACACTCTAAATCCATGGTGCTATGCTAAGCTCTTTCTGTAT
 TTTATCTCATTTGATATTACAAATATTTGATGTGTTAATAGTAATGACTA
 TCTCCATTTTTTACAAGTAAGGAACTGACATTGAGAGATTAAAAGACTAG
 CACAAATCACAAAGTAAATGAGATTTGAATCCGGTCTTGATTCCAACTC
 TACAGTATTCTAAATTCAAGGAGACTAAATTATAAGATGGAGAGCCAATT
 TTAATTTATAACAGGGTTAGAATGGCAGAAGAGACCTGACATTCACACCT
 CTAGCCAGTGCATCATCTTCCTGTAGGCAAATATGCAGGAAATCTATAAT
 AAGAACGTCCTTTGGTGAAGGCCAGGTGCAGGGGCTTACACTTGTAATTC
 CAGCACTTTGGGAGGTCAAGGTGGGAGGGTCGCTTGATGACAGGAGTTTG

FIG. 3 (9 of 52)

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AGAACAGCCTGGGCAACA TAGTGAGAC TGTCTCTACAAACAAAACA
ACACAAAACAACCTTCAAGAAAACCTCTTGGTATGGATCAGAACAGATG
AATTATCTATCTGATCCAAATGCTTAATGACATTAAGCCACAGTCCACTC
ACTGCCACAATAGAGATATACCTGCCAATGCCACTCAGGTAATCCCATCA
AAAGTGGTAATGAGGTCTGCAGCATGACTTGTTCTTAGTGATCCCAGCCT
GAGACCTTGAGATTGCAGCATTTTATTCTACATATGCACAAAACATCTGT
TGAAAAATCTTCTAAATTGATGCAATACATTTCGTATCAAGAATACCTGTC
TGTAATCTCCATAAACCTCTCCTTTCTGTTTTAAAAAATAGTAACAGCA
TTTCTCCTTACATGACAAAGAAATGACTTCACCATCTACGAAATAGTGAA
TAGGAGCTGTGTGGAAGGAAATTAGCTCTACTTCTTGGTGGAGATGAGAA
GGGAGTGTTCCTCTGAAAATCAAGGCTCTTGTCTATGCTAGGAGCCAAAGT
CGTTTTTTAGAGTGTGGACAGTTGAGAAGATAAGACAGGGACCATCCACT
CATGTTTTTTCTTATTCCATAGGCCTCTCTCAATTGGGCAAAGCACTCCAG
ACCTTTTGGAAAGAGTGACACCAAAGGCAAGCACCTGCTTGGCAGGCCCCCT
CAGCTTCTACGCAAGTATAAGTGAGTATATAAAATGGGGGTACTTGTGCT
GTTGAGTACCTTATTTCCAAATGAGGCCTGCCGGTGTCCCTGTGGCTGTG
AGAAGGCCTCTACTGGATAGGTGGAAGTTGTGTGTTCTCATCTTTTCTAA
CCCTGGATTGACTTGCCCAAAGGAAGCCATTATTAACACTATAATAAAA
CCATCCTTAATCTGGGACTCTCTTCATGCAGTGGTTCTTAACCAGTGATA
AACATGAGAGTTACTTTTGGAGCTTAAAAAAATTAAGATGCTCAAGGTCT
ACCCAAACTGACTGAATCTCCAGAGGTGAGGCCCAGGGATGTATACTTTT
GAGCCAGACCTCAGTTTACCCTGCAGAGCTCATAAGGTTGCATAACACCC
TTTGTGAGCCACTCTGATGAAAAGAAAAATTGGTGAGGAATAAGTTTTAG
AGAAGAAGGAGCAAAGGTGTTCTTGGCCAGTGAGAGCCAATGACAGGGAA
ATGCAAACAATGTATCCACAAGAAAGGTAAATTACCCTATAGAGCATTTT
AGGATAAATGAACATCTCATGCCTAGGGTTGAGAGAGGGTACAAAAAAA
AAAAAAAAGAGCACTCTGGATACACAACGCGATAAATGGAATAAAGAA
TTTTTTCCTTGTAATTAAAAAAATCCTTTGTTACTGAGGTATAATTTAA
TCTATTTTATGTATAGTTCAATGAGGTGTTATAGATAATAAATTTTTTTT
GTAAATTATTATATTGTCATATACTCATACTCATTTTTTTAAAGTCAGA
AATGTATATAACCATTAACTTATAAATCATTGAGTCATTGAGAGATATA
GATACACGAGCATATTTTATATCCACCACAATAATTATTACCATCTCAAC
AATTCCATCACCCCTCAAATTTCAAGCGTAGGGGTTTTTAAATGTCAAAG
GAGTCTACTCAGTGGGAAGAAAGTTAAGGAAAAACCTTTGGGGCTTTGG
GCTCCTTCCCCCTGGGGTTAAAAAGGCAGGAATTTGGGCTTACCCCCCT
GAAATTGGGAACCTGAAATTTTGGGAAGTTTAAAAAAA

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TCAAGCAGCCTTCCCTTCCCTTGGCTTCCCAAATTGTTGGGATTACAGGCAT
GAGTCAGGATTCTTGGCTTAGTTTACATTTTCTAGAGTTTTGTATAAATG
GAAACATACAGAATGTATTTTTTTGCGGAGTGGGGGAGTGTTTCTATTTC
TTTCTTTCCATTTTCCCCCCCCCNCCCCCGAGACGGAGTCTCGCTCTG
TCTGTTGCCCAGGCTGGAGTGCAGTGGTGCATCTCGGCTCACCGCAAGC
TCCACCTCCCGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCTGAGTAGCT
GGGATTACAGGCGCCCGCCACCACACCTGGCTAATTTTTTTTGTATTTT
GGTAGAGACGGGGTTTACCATTGTTAGCCAGGATGGTCTCGATCTCCTGA
CCTCGTGATCTGCCCGCTTCGGCCTCCCTAAGTGCTGGGATTACAGGCGT
GAGCCACCGTGCCCGGCCCAAGTGTTTCTATTTCTTAACCAGCTTTCATG
CAATCTTTTTTTTATTTTACCATTCTGTGATCCCACTCCCAAAGGTACTA
GATGTCGATTGGTCCTTAGGATCAGCTACCATTTGCCCAACTGCTTTCCA
GCCTTCCAAAATTTTTTTCTTTTTTTCTTAAAGATACTCCTGTGTGAGG
CTCAGAACTCTTGAATTGCTACTGCAAAATATGAACTCGGTGATGTGAATG
CCAGGGAATTGCCTGATTGATCAAAGAAATGTATCCCCTTCTCCCTCACT
CTTGCTGTCTTCTCATTTGTTTTCCCATCCTTGTGGATTCTGTGAATTTA
AATATCCCTTTAATGTTATAATATTTAATGGCGTTTGGCGAAAAGTACA
GAATTAGGTGCAAGAGTGATAGCTGTTATTTTTTTTTTGGCCTCTGAGA
CTGTTTATATATGCAAGTTATTTAACAGAAAGTTCTGCAGTGACCTGAGA
TGTCAGGGGGGTCTGATAGAGTACGTTTGAAGGCAGTTACTGGAAAAAA
TAATGCCATTTCTGGTTTGTACTTCGGTAAGTTCAGATGACCCAATATAT
TGTTTACATGTGGCATTGAGTAAAAAAGTAGCTTCCCCTCCCTTTCTTCT
TCCTTTTCTCCTTTCCTGCTTCTATAAAGCATCTGCTTTGGGAAACTTCT

FIG. 3 (10 of 52)

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TAGGAGGAGAGCTTGCCAGCCCGTGGC...ATGGAGAGGTCTTGAGAGAG...
 AAAAGAGATGCTCCCACTCAATGCAGGATGGTGTGGAGGTAAATGGGGAT
 ACGTCTGGCATCACTCAGGAATGGGCCTTCCTGGCAGGGAAAAAAGGGA
 GGGGAAAGAGGAAGGGAATTCNNANATNAATTGCTGAATACGGGGATTCC
 ATGGCCTGGATCCAGGAAGAGAACTTTGGGAGGTGTGAACCTGGAAGGCA
 TCANCTGATGAGGAGCAGCCTGAACTCCGGGGAGGACCTGTTTTTGGTGG
 CCCGGAAAAAATGCCTTCCACACACAGGGAGGCCACCCGGCTGATGGGC
 TGGGGGTGGACGGACAGCCCTAGGACAGGCTTGGGAAACCAGGCTCAGG
 TAGGGCCTGCGAGGTTCTCGCTGCGTCTCTTTCCTTCCTGGTCTTAGAAA
 ATAGAATCCAAGGCCTCTTGAGAGTGGAAGGTGGGTGGGAGGAGGGCAG
 ATGGGGCTTAGGCCAGGACACCCGTAGAGCTACTGCCCAGCTGTCTCTC
 AGGGACTCTGCTGAGGTCACTCCAAGGATCATTCTTAGCCTTGCTAGACA
 GTACTGACAGAGGGAACCGTAGTATCGCACCCACTTCCTTCTCTTTCAAT
 GAAAGTTTAAAGGTCACCATTTCTCTGGCAAAGGAAGTTCCACAAATAT
 TCCATTTCCGGTCTTAGAAACAGCAAGGTATCAAGCAATTGCAAACCTTCC
 TGTGCTGGGGAATTCCTCAAGGAAGTAGGGGCAGAGTTCTGGTGGAGACAA
 AGTGAATTCCGAGTGATTAGTCAGTAGCAGTAGCAGTAGCAGTAGCAGTA
 GCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTA
 AGAATTTCCCGCACGTGTCTCAGGCTCTCATTGCCAACTCAGTCTCTA
 AGTATTTTATTGGCAGGAAAAATAAAATAGCTATGAGTGAAATAATTCA
 TTAGACCTGAGCCTCCATCAATTTTGTGTTTAAAGGCCTGACTCTCTTTA
 CCTTTCCTGGGATGGAAGATGCAAATGTTCTGATCTCACTGTCAAAAA
 AGAAGAACCAGTGGGTATATTGTATGCTTGAGTTCCAGCCATTAGTCACA
 AGACATAGAGATGACTGCCATGTGTGTAGACTTTCTATAGACTGTGTGCT
 AAACCCGACCTGCCACTTCCAAGGAGTAGATGAGGAATGTCCATGGTTCT
 GGGGAGCCCTACCCCAATTTGGGGCAGACATTCCAAAGCTCATTTTCTGT
 GGAGGGGGTGGATGGTTAAAGGAACGGCTGGGATTTACTCTTCTTTCTAG
 GGCCAAGAAAATGACATGCTGCCTCCATGTTTAATCATCCTTCCCCCTGT
 TAATAACTATGGCTTTAAGTCCCCGGTTAGGGCCTTCCTCCAAAATTGGG
 GAAAAAATTCCCCTCCCCCCCCCTAAAAATTTTTTTTTTTAAAAAACCTTT
 TTTTTTGGGGGTGGGAAAAAACCAAAATTTTTTTTTTCCCCAGGGGTTT
 TTTAATTTAAATTTCTCCCCAAAATTTGTTTTTTTTTTTCCGCGAAAAA
 AAGACCCCCCAAAAAAAAAAAGTTTTTGGCGGAAAAAAAAAATATTTTT
 TTTGTGTTAAGAAATGGAGAAGAAGGGGGTTTTTTTTTTCTTCTCCCCC
 CACCCGCCAAAGGAAAGGTTGTTACAGATTGTTTTGTGTCTCCCGCCCA
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ATGTGCCTGCGAAATCATCCTTCCAGAAATATTTGCCCTTTCTTTTGTT
 ATAGAGTGGCACTGCCCTATATGGTGACCACTTGCCACATGTGGCTGTTG
 AACACTTGAAATTGGCTTGTGAGAATTGCAGTGTAAGTGTAACACAT
 ACCAAATTTCAAAGACATGGCACATAAAAAATGTAAATATCTCATT
 AACAATTTTTATATTGACTGTGTAAGTAACATTTTGAATATATTGGATTA
 AATACATGGATGATGCCCCAACCCACAGTCCCTTATCAAGTCTCTACT
 TCACATTTTTGTACTTCTGACTTAGAAATAGCACTGGCGTCTAAGAGCCT
 ATTAATGTCGTCAATAGGTTCTTGGGAACCACAATTTTAAACAAAATGAC
 ATATAAGAAAACGAATAACATTGAACAAAATGACATTATTCGAGGACCTG
 CTGCATGTTGTTTCACTTAAAGTCAGTGTCGAAGAACTATCAGTGACAT
 TTAGTGAGGAATTGCTGTCCTTCCTGTTTACAGGAACCTGGGCAAGTTAC
 TTAATTCCTCTAAGCCCGGTTTATATCCCTGCAAAGAGAGAAGGATAATA
 ATCACCAGTACTTAGTGATGTGTAAGGAGAAAAATAAAATAATAATATG
 AAATGGCTGACAGTGTCTTGTACACAGAAGATGTGTGATCCACAGTAG
 CTGCTATTGTCTGCCTCACTTCACTAGTAATGGTCCAGGGAGGCCTTTAA
 TGTGCATGGTGCAGTACATTACATGTTGGACATGGGTGAAGGGAAAGAC
 CAGGCTCATCTAAACACAATAGGATGCTTGTGGTGTTTTGAGGAGGAATC
 AAGGACTAGTTATCCACAGCTGTAACATGCATGGATCAAAAGAGATAAGG
 CACACAAAAGACTTTGTGAGTAGCAAAGCATTACAAAATGCAGAGACCAG
 CTGTGGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT
 GGTCTGCGCAAGTCACGCCATCTGTCTTGATGCCCTTCCCCATCTATAG
 AGAGGGAGCAACTGAGGCCCCCTTCCAATACTGAAGTCCTTTATTTCTGCT
 ACTTTAGAAATATCCACATTTTTTGGTAAATTCAAATGATCCAATGATTCC

FIG. 3 (11 of 52)

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ATTCCTAATGTTCAAAAAGCCCCA AACATCTAAATGAATCAAAC
AATAAAATATTTATTGTGTATGTTTTGATTGCTGAAACTTCTATTTTAGC
AACACACACACACACACAGAACCCATAAGCCTTCATCTTTCCTTGGAT
AAACGAGCCTTCCTGTCTGGCCATTTAAGTCACGATTAAGTAAATGATT

AATAAACTAAGATAAAAGGAATAATTAAAACTTAATTTAAAAGAAACA
GGAAAGGAAGCAGTTACATTAAGCAAAAGAGACATCTTCATGGTTGAAGA
AGTGTATGCCCTGGTGTCTGGATCCCATTTAGGAACTTGGTAACCTTGC
AATCTTGGGCAGATTGCTTAATTTCTCTAGACCATGACTTCCTCTTCTGT
AAGATGTGATAAGAACAATCTACCTCACAGGTTTCATGAGAGGATTAAATG
AGATAATGTATTATAATCCCTTGAACATGGTAGGCTGTTATGTTAAGTCC
TTTCCTCCTTCTCTGTAGCTATCATGGAATTTAAAAACACATTATACTA
GAGCATGAGTTGCGACTAAAGGCTCAATTGTCTCTGCATGTGTTGGCTCA
TGCATGCTTTATTCTCTGAAGAGCTTTTATACCAAGTGAAAGGAAATAA
TTGCATTTCCCTGAAAATTCACAGGAAAAAGTTATGTTTTTCTCTTCATT
CAAGTGATTCTGTTAGACCCAACCACATGCAACAATTTTAAAGTTGCTTC
CAAATATATTTACAAATATTTCTGTCTTCAAGGAACAATGGCAAGACCA
TGACTCAGGTTACATCCGGATTCCACCACTAACCATGTACCCAATTACT
TCAGTCACCTTCATTTCAGGTCTTACATATCACAGAATAAAATCAGATTTT
ATCAGAGGAGGTGAAGACAGGGAGAGGAGATATTTCAATCCCTTCTCCGC
AACCCCGTTTTTTTTTTTTTTTTTAAACAAGGATCCTAGAGTTACTGAATG
ATAGCACGTTTGAGGGGGAAAGACCCTAAGGATGATCTTTATAAGCCATC
ACTTGGTGTGGTGGTGATAAAAACTCGAGTATCTTTATGCAGTGGAAA
GAGAAGATTGGAATCAGAAGCTTGAGTTCAAGCACTGGTTTCAT
CAGTCTTGTGATCTTGGGTGGTCACTTAACCTCTTCAAGGGTCCTCAGC
TGTGAAAGAAGATAGTATCAGCTAATTCTTGTATGTGCAGTGAGGAGGCA
GTGAGATAGTGACAGGTAACTATAAAACAATTGTACATGAAACGCATCA
CAGTGATTCTTTGGACCCACAAGCTCCAATCTTATAAAACATATCCAGTC
ACCCACCAACATAGATCATCTCACCTTGATATCTGATTTTGTGGATCAT
GGGGAAAACTGCTGATTCTTAGCAAAACCCATGGCATAGGATAAGTGCA
CAATAATTTTTTTTTTCTAAATGATTTAGATGACAGTGAATTAAGGG
TTTCCTGAGGCCTCCTCAGAGTCGAGAGGTGGGTGCCTGAAGCCACCCAA
AGTCCCTGTCACAGGATGGCTCCCAACGCACACACCACAGGCCTGCCCAG
TATGTTCCACTATCTACCCAGTAGAGCCCTGCCCAGTACGTTCCACTGTC
CCTTCCCTAGAAGAGGTGACTGTTGTTACAGTCCCAGAAAAGCGGGCTC
CCCAAAACAATGCAAGGACCCACCTCTCTCTGAACCTCACCCACCTAGT
TTTCCTTTAAAATCAATTTACAAGAAGATCATGTGAAGGAAAAGGTTGG
GTGATATTCTAACCCAAGTTAGCTGTTTCTCAACCAAGTTCTCTTTGAAA
AATTCACAACACCTTTGGGGGAATTATTTACAACAGAGGAGTGAGGATG
GGACCAGGATAGGTATTGCCTATGTTGGTGGAAACCAGGGTTTTTTTCTG
GATTACCAAAGAGATGGTATGCATTGCTCCCAGAAGCTAAATATCTTCAG
GCTTTCAATGGTGGCCTTCACCTGAAAATGTTATCCCTGTTGAAGCTTTC
AAGCCAGTATTTTCATAAGAACTATATTTCTTTGGTGAAGTGAAGGCATT
ATAATGATGACTATACAGGTTCTTGAGTGACTGAAGCCATCATTAGCATT
GTCATTATTTTGTGTTAGTTGCATCTCCATAGCAGCTCACATTCACAATG
TGCTTTGCAATTGTTCTTAGCAATAGCCCTCACAGATTCTCAGGAGGA
GAGGGTTAATCCGGATTAAACATTTCTGTGAAGCCTAGCGAGATTAATCGC

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AAGAGTTTTTAAATTAAGTAAGGACGCCGGGAAACAAATCAATCCCAGCA
AACATTTTGTGTTGGGATTTATCATTCAAGCAATTTTACAGTTATCCCTGTC
AAATACATTAAGTGTTCAAAATTGGGCATAGGGGGAACAAAATAATAAAC
CCAGCCAAAACAGAATAATCCCTGTTTGTTCATGTTGGATAAAAAAGAC
ATTACTATTGGTGTAAAGGAATTAGATACATCTTCCATTATTTAGTAAAA
TTACCATAACTTCTAACTTTGTGGCTTTAGGCAGTCTAGTCCACAGGCAG
GAAGGAGGTTTGTGTTTGGCAAATGACTGTTATCATCTTCTGTTTCAAAGC
TAAACCATAAACTAAGTTCCTCCCAAAGTTAATTCAGCATATGCCAGGA
ATGAACAAGGACAGCCTGGACGTTAGAAGCAAAATGGAGTCAGGTAGGTC
AGATCTTCTTCACTGTCTCAGTGATGGCAGTTTCATAACTTTAAATGATG
GCTATCACAGTTTTTATAAATAATCTAGATAAACAGTTAAAATAAAATAA
TTAGGTAAATGTAGTGCGATAAATATTAGTAGACAACTCACCATAATTT
AGAATCTAAAGTTAAATTAATAATAATATTTTATTATTTGGTATTTTCC
AAGAAAAACATATTGTAGGAAACCATTCTTTTTTAAAAAAAAGTGTCCT
TTTAAAAAGGTGAATAATTTTGTCTAATTCAAAGTTTATTGAAAAGTTA
TGTATAAAACAAGGTAAAAGGAACAAGGAAATAAGGGAAATGTAAAGAAA

ATTATAGAAATAAAGTGCTATTTTTTTGGTAAGAAAGCTTAAAGAGAA...
ATTTTAGGTAAGAAAGAATCTTACCTAAAATTTTGTGCTAGAATAAAGTG
ACTGGCTAAGAAAGGGATGTTCAAAGCTATTTATGACAAACCCACAGCCA
ATATCATACTGAATGGGCAAAAGCTGGAAACATTCCCTTTGAGAACTGGC
ACAAGACAAGGATGTCCTCTCTCACCCTCCTATTCAACATAGTATCGGA
AGTTCTGGCCAGGGCAATCAAGCAAGAGAAAGAAATAAAGGGTATTCAA
TAGGAAGAGAGGAAGTCAAATTTTCTCCGTTTGCAGATGCATGATTGCAT
ATTTAGAAAACCCCATCATTTTCAGCCCCAAAACCTCCTTAAGCTGATAAGC
AACTTCAGCAAAGTCTCAGGATACAAAATCAATGTGCAAAAATCACAGGC
ATTCTTATACACCAATAATAGACTAACAGAGAGCCAAATCATGAGTGAAC
TCCCATTCACAATTGCTACAAAGAGAATAAAATACCTGGGAATACAACTT
ACAATGGACATGAAAGACCTTTTTCAGGGTGAAGTGCAAACCACTGCTCAA
GGAAATAAGAGAGGAAACAAGCAAATGGAAAAACATTCCATGCTTATGGA
TAGGAAGAATCAATATCGTGAAAATGGCCATACTGCCCAAGTAATTTATA
GATTCAATGCTATCCCCATCAAGCTACCATTGACTTTCTTCACAGAATTA
GAAAAAACTAATAGCCAAGACAATCCTAAGCAAAAAGAACAAAGCTGGAG
GCATTGTGCTACCTGACTTCAAACCTATACTACAAGGCTGCAGTAACCAA
ACAGCATGGTACTGGTACCAAACAGATATATAGACCAAAGAACAGAAC
AGAGGCCTCAGATATAACACCACACATCTACAACCATCTGATCTTTGACA
AACCTAACAAAAATAAGCAATGGGGAAAATAATTCCTTATTTAATAAATG
ATGTTGGGAAAACCTGGTTAGCCATATGCTGAAAACCTGAACTGGACCCCT
TCCTTACAACCTTATACAAAAATCAACTCAAGATGGATTAAAGATTTAAAC
ATGGCTGGGCATGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCC
GAGATGGGTGGATCATGAGGTCAGGAGATGGAGACCATCCTGACTAACAC
AGTGAAACCCTGTCTCTACTAAAAAATACAAAAAATTAGCTGGGCATGGT
GGTGGGCGCCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATGG
TGTGAAACCAGGAGGTGGAGCTTGCAGGGAGTGGAGATCACGCCACTGCA
CTCCAGCCTGGGCAACAGAGTAAGACTCCATCTCAAAAAAAAAAAAAAAAA
AAAAAAAAAGAAGGATTTAAACATAAGACCTAAAACCATAAAAACCATAGAA
GAAACCTAGGCAATACCATTTCAGGACATAGGCATGAGCAAAGACTTCAT
GATTAGAACACCAAAGCAATTGCAACAAAAGCCAATTGACAAATGGGAT
CTAATTAACTGAAGAGCTTCTGCACAGCAAAAGAACTATTGTCAGAGT
GAACAGGCAACCTACAGAATAGGAGAAAATTTTTTCAATCTATCCATCTG
ACAAAGGGCTAATATCCAGAATCTACAAGGAATTTAAACAAATTTGCAAG
AAAAAAAAAACCCATCAAAAGTGGGCAAAAGATATGAACAGACACATCTC
AGAAGAAGACATTTATGTGGCCAACAAACATGAAAAAAGCTCATCATCA
CTGGTCATTAGAGAAATGCAAAATTGAAACCACAATGAGATACCATCTCAT
GCCAGTTAGAATGGCGATTATTA AAAAGTCAGGAAACAACAGATGCTGGA
GAGGATGTGGAGAAATAGGAATGCTTTTACACTGTTGGTGGGAGTGTGAG
TTAGTTCAACCATTTGTGGAAGACAGTGTGGCAATTCCTCAAGGATCTGGA
ACCAGAAATACCATTTGACCCAGCAATCCCATTACTGGGTATATACCTAA
AGGATTAGAAATCATTCTATTGTAAAGACACATGCACATGTATGTTTATT
GCAGCACTATTCACAATAGCAAAGACTTGGGAACAACCCTAATGCCCCACC
AATGATAGACTGTGTAAAAAATGTGGACGTATACCCCATGGAATACTAT
GCAGCCATAAAAAAGAATGAGTTCATTCTTTTGCACGGAACTGGATGAAG
CTGGAAGCCATCATTCTCAGCAAACCTAACACAGGAACAGAAAACCAAACA
CTGCATGTTCTCACTCATAAGTGGGAGTTGAACAATGAGAACACATGGAC
ACAGGGAGGGGAATGTACACACCAGGGCCTGTCAGGAGGTGGGGGGCAA
GGGGAGGGGATAACATTAGGAAAAATACCTAATATAGATGACGGGTTAATG
GGTGCAGCAAACCACCATGGCACATGTACACCTACGTAATAAACCTCCAT
GTTCTTCACATGTATCCCAGAACGTAAAGTAAATTTAAAAAAGAAAGAA
AGAAAGAAAAGGATGTTACGACAAACCAGAAAGTCCAAGCATGTTCATGA
ATAGTCTGTGTAAGTCACAATAAGAGGATTTATTTAAAAAACTTTTATA
TGATAAAGTTGTCTATAATTAAAGGGAAATTATAATGGTCTTTCTAGAGA
TTGGGTTGATGTTAAAAAACTACTTATATATTAATAAATTTGGTTAGAAC
ATGAAATTTTCTTACGGGGTTGATTCACCTCTTAATAAATTATAAGAGACT
TAAGAATTTTTTTTTTAACCCAAAGTTCAGCTTTTATTGCATCTTGCTGTT
TTAGGTTTTCTCTCCCCTTTAAAAGGGTGGGAAATAGTAATGCCCTCCTT
CAACTCCCTTCAGCTCATATACGTTTTTTTACCCTCAGATTCTGTTTGTTG
TGTCCTGATGCTAACAATGTTTTCTTAAAGGTCTAAAGGAAATGTTTTCT

FIG. 3 (14 of 52)

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TCCAACATAATATTCTG1GCATTGCAGAAGGTCTTTTCTTTTGCCTTTTG
GTAAGTGGCTTAACAGATTTTATGTTTTATTGAAATAATTTCTATGCCAT
TATTATTAAGTTTTGGTTTGCTTAGAAAACACTGAGATTAATAACAATTTT
TTAAAAATTATGATTATTACATCCATATATCTTTATGTATGTGCTTTTAA
AGTCCTTGTGACATTGAGTTCTAGGGCTTGACTCCTGGGTCTTAAAAGGA
CAAGTCCTGCTAAATCTTAAATACTGACAGCAATTAAAGGCTCATCTTCA
GGACTGGTAGAAAATGCCAATCAAAATAAACTGCATTCTTGAAACACAGA
GCCAGAAATTAAAGCTATTCAACTCAAGGCCCAGGAAGTATAGTGGAAGA
GGTGGGTGTGTGAGATTGTAAGGGCCAATTTTGAGAGATAAAATAAGTTC
AATTTCTCTATAAATTAATCATAATCATTGATGTCCAAGCCACACTGATG
CAAGATCAGCATATGGGTCTGTGTGAGATTAAACAAGGTTTTCTTGAAGC
ATTAACCTACTCCTTAATAAAGGTTATAGAGGTTATAAAAGGCTTCTGGA
AGTTATAGCTATGGTCAAGATAAAAATTTCATAGATTGTTAATAACAATTT
TGGAACAAATTTAATTGGCTTCTTGCTGTTTTTATTAGGGCTTATTGT
TTGGAAATTAAGTCTCGTCTCTCAAAGAATGAAGGCTTTCACCTTTTTT
TTTTTTTTTTTTTAATCCTTGAGTTATCACTTTGGTCAAATGAATGACTTA
TTTTACAATGACCTTTCATCAAGTGTTTTAAACCTTTCAAATTTGACAAA
CTTTCCAAATCAAACTACAAATTATGTCTTTTTTATGACCTAATGAATCC
TTTAAATACTAGGTTCCCTAAAGTCCAAAAAATAACATAA
TGTGGCTTATTTGGTATAAAAATTTTACAAGAAACATTGTCAAATATAAA
ATATTGTGTGGTTTTGTTTGGGCTGTATTTGTATAAATATGTTATTTGGTA
TGTGTTCCAAATTATAGGAACTCCTATAATTCTGATATGACTTGGTGT
ACATTATCAGTAATAATTATAATTGTTATGGTAAATTATTGTGTGCCATG
GAGGTAACAAATTTCCCTCATCAAGTGTTCTTTGACTATGGTTGCCCTAA
AACTTTTTGCCATTACAGACAATTGTCTTGCTTTGGTCTCTTTAGAAG
GTGGTTTTATAATCAGCTATAAACTCTAACGGGTGCTCTTGAATGCAGG
CTTAAGATAGCTTTGGGAGCTGTGACATCAGAATAGAGGAAAACTTTCA
GTATTCATGGAGTGCTGAAATATTATGAATATCAAGCAAACAGGAATT
AACTTCATAGATGGAAGTAAAGAATGCTGAAGTAATCTTTTTGACTTTT
TTTCTTAGAATGTTGATCCTTCGTTTTGTTTTTCAGAGTCNAGGAAATTT
TTCTGTTGAGATATTGACAGCTTTAACAATTAAGTATACTCCAGTGAACA
CAATTTGGAGCA

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ATCTAGTCATTCCCCAGCCTGACCAATTCAATGGCCCCCATCTTAGTTAA
AATTCCTCACCTGACAAGGCCCATCTACGCCTCTGACCTCATGCCCTC
CACTCTCAGTCTTGCACTCACCTGCCACACTCAAGGGCTTCCCCAGGT
CCTTCTTAGATTCCACCGATAGCTCAGGGACTTTGCACATGCTACGGTCT
CTGCCTGGCTCCTCCCCAGATCTTCTCATGCCTAGCTGCTTCTCATCAGC
ACCCCTCAGAGACTGTCCCTGCCCCACCTCTCCAGGTTCCATACCTGCCA
CCCTCCCCCAATCACGTAACAGTTTCTTACAGAGCGAGTTACCATCCCA
GTATTTCCCTAACTTATTTTTTGTGACTGGTCTGTTGCCTGTCTCCACCA
CAAGAACATAAGCTGCATGTGAACAGGAGCCTTGTCTATCTTGTACCCC
AGTGGCTGTGACATAACCTGATACACATTAGATGCTCAATGATGTTTGAT
GAATGAAGTGCTGGTAGTCCAAGTGTGTTTCTTGTCTGTGTAAGTATGT
CTGTTGTGGTTTCTAAGAACCTACAGCTCTCCACTGTGACTCCTGTTT
TATGGTCTGATTTGCTGGACTAGAATCCTAACCTACATGCTTACTCTTA
GTGTCCTCCCCCAGAGGCTGAATCCCAGTCCCTAAACCTCCACCAAATGG
CTAAGACCTAGCTTCCAACCAGACAGGCTACGCTGAGACCTCAGCACCG
CCCTTCTGCGGTCTCATCCTTAACGCATCCTTCAGGGCCCAGCTTAAATG
TCTCTTCTCCAAGGAAGGCTATCCTCTTTCTGCCCCCTCAGTGCTCTCCAT
GCCTCCTCTATGCCTCCATGCCTGCTTTCAACCCTGCAGAAGTGGAGAAA
TTGCTAATCTGCTGTGTTGACACTGTGCTGGGGTGCTTGGGCCAGGGAG
CAGGCTGGTGGTGTGCTGATAGCCCGTGGCTGTGCCCAGGTCCATGCTCA
CTTCTGAGCCCCAGTGGAGTAGGCTCCCTTTCCCTTATTGCAGCACTCA
GAGGAAGGACGTGCTTCTTAGGACAGATCTGGCCAACCTCTCCCTCGTGA
GAGAAGGCCAGCCATCCTCTTGCCCTCTTTCTTTCTCCTGCCCCCGAGT
AATAAAGGTGCCTGGTCAGAGCCTTCTAGAAGGAGACCCAAACATCCACC
ACACATTCCCAGTTCCAACCGTCATCCACATGGCTGGCTGTGCAGGTAAA
CGCAGAGTCTGTTTACACACCCCAACCATCTAGTATTGGATGGGAGGACA
GTAGCGTGACACTCTTCTCCAGCCTTGAGCCCTACTGTGGGCCCCACCCA

ACCCAGATACCAGAGGAGCCCTGTACTGGGATGCTATTGGATGCTTGTGCT
AGTCATGTACAAAGTTAGCCCTTTGTTATATAGAGTTAGCTACGTACATC
TTCCTCTGTAGGGAACCCAAGAGGGGAGAAGAGATATGTAGTAGGATTTA
ACCTGCAAATCCTCTGCTGAGCACCCTGCACTACATACAGTGGGTAGCAT
GTGGTAGGTGCTCAATAACTATTGACCGATAGATTGAATACAGGTAGGAT
GGTGACACAATCTAAGATCCCAGGGGTGGGGAGACCACACGCTTGGTTAG
GGAGACCCAAAGTGGACCGTGTGGCCAGAAGAGTCCCGCACTGCACTCTA
GTGACAGTGCAGAAAGTCACTGTGGGAAATCTAGAAGTTTCTACAGGTTG
CTATTTTCATCATAGCACTGTGCAAGGCCAACCTTCCTGCTCCACTGGCTG
TTGGGAAAAGCTTTCTCTTTTCTTCCTAGCCAGGGAGCTCTCAAAGTGTT
CCACTCTCTCACCTCCACCCAGGCGTCCAGGTGTGGAGGACACTTGCCGG
CTGCTTGTCTGCTGACTCATCCCTTGGTTTCACTTGGAAAACCTACCACC
AGCTGGCCTCTTTCCAAGCATCAGCCTCCTCATTTTCTTAATCCCTTAGG
TGTGATCTCACCTCCACACAGTAGATTGCCTCAAGGCCCAATTCCAATAT
GAATAAAAATGATTATTTTGTTCATCTTCCAATCTTCCTTTTAAATATTA
TTTTATAATTCCCTTTTAGGAGGATCACCTAAGTGAAGACTATTTTACCT
AAGAAATGTTAAATGTAAAGACATGGTTGTAATCTGGGGATTCTCTGTTA
AAATGGCTAGCAGACAGAAGTCAGACGACAGGCTAGAAATGTGTGAAGAG
TGGTTGCCTTTGAAAGGCGGAGTTGGTAATGATTTTCTTCCATTTTCCA
TGCTTTCCAATTCTCTACAAAGGCCTTAATATTACTTCGATAACCAGGAC
CTCTGATAACCTGCCCCCACCAGTAAAGACTTAGCTGGGAAAGTCAGCT
TCATGTGAGGTAAAAGGAACCAGGTAATACACAATTCCCACTGCCAACTG
TCGGGTGTGCAGGCCTGAGCTTCTGTCATGTGGGAGGAAAGAGAAAGAAG
AGAGAAACTCCAAGATCCAAGAGATCCAGCAAGAAGGCTGGAGTCTGAGG
ACGCAGAAAGCTGAATGGCACAGTTACCCTATTGTGCTGAGGTTCTGTG
GCCTCTGGGTCTCTTGACAACCTGGGCAAAGACCCACAGAAAACCTATCTCT
AGACCCTACCTGTGGGAGGGGAAAGTGCTTAAGATCATTTACAGGACAGC
CACCTGGACCTCAAATGGCTTACAGTTCCCTTCATCCAGAGGGTCTTCATT
TAGTACATACCAGGTGCTAAGCTGGGTGCTGGAGACATGACGGGGAACCC
ATTTACCATGGCTTTGTTACTGTGACATTCACATCTAGGGAAAGCCAGCA
AAGGGGAGGGATCGAGGAGAGCTTGTTAGGCAGAGAAAATACCCAAGGGC
AAGGGAGAAGCCAGCCTGTTCTGAGCACACACAGTGGTTCCATCTAACTG
GGCCTCAGTGCCAGGTTGGACTGGAGATGGGGCTGAGGAGCTGTCACAGA
GCATTCTGGACACAGATGTACATAGTCCCTTGAGGTTAGGGTCTTAGG
CATGGCAGCATTGCTTTGAGTTTTTCTTTTGTAAATGTTGCCATTTCATGA
CAATGTGGAAGATGGGTCTTGCAGAGAAGGGCAGGGCTGTGAGACCAGT
TAGGAGACTAAGATGTGAGCCAAGGAAAATGAGGAACACCTGAACACTGG
GGCAGGTGCAGGGCCCAGAGAGAAGCAGATGGCTTCTGAGGTTTTAAGT
AGGTAGAATCAAGGCAGCTGGTACAGATCTTTTATTACATATAAACTGGA
ATAAGCCATCTGTTCCAAGACAAAAGAGTAGGCGGAAAACAATACAAGAC
AGAAATGGAATTAGAACAACCTGGGAGGAATGTGGAATTAGAGTAGAGA
GTCCAACACTGGCTGCAATCATAAAAATGTAAACAAACAAAATTTGCT
AGGTGTGCTTACTTAGAAATAATTAGCTGTCAATTAAGTTCACTTGTGT
TATGGCTTAAATGTGTCCCCCAAATGTGATGTGTTGGAACTTGATCCC
CAATGCAACAGAGTTGAGAGATGGGACCTTTAAAAGGTGATTAGGTCATA
AGGGTTCTGCCCTCATAAATGAATTAATACTGTTATCATGAGAGTAGATT
CCTGATAAAAGGATGATCTCTGCCTCCTCCCCACAGCCCTCTTGTGCATG
CTTTCCTGCCTTTCCACCTTCTGCTATGGGATGACACAGCAAGAAGGCC
TCACCAAATGCAGCTCCTTGATCTTGGACTTTCCAGCCTCCAAAACCTGTA
AGCCAAACAAATTTCTGTTTATTATAAATTACCCAGTCTCAGGTATTCTG
TTCTAGAAACACAAAATGGACTAAGATCATTAAATTATCATTTTTTATCA
GACTGTTGA

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AAAATATAACAGAGAGTAAGAGGAAAATTACCTTCTTTCTTTTTCCTTTC
CCTGCCTGACCTTATTCACCTCCCATCCAGAGCATCCATTTATTCCATT
GATCTTTACTGACATCTATTATCTGACCTACACAATACTAGACATTAGGA
CAATGTGGCCTGCCTCCAAGAACTCAAATAAGCCAACCTGAGATCAGAGA
GGATTAATCACCTGCCAATGGGCACAAAGCAACAAGCTGGGAGCCAAGTC
CCAAAATGGGGCCTGCTGCTTCCAGTTCCCTCTCTCTGCATTGATGTCA
GCATTATCCTTCGTCCCAGTCCGTCTCCACTACCACTTTCCCCCTCAA

CACACACACACACAACAGCTTAGATGTTTTCTCCACTGATAAGTAGGTG
ACTCAATTTGTAAGTATATAATCCAAGACCTTCTATTCCCAAGTAGAATT
TATGTGCCTGCCTGTGCTTTTTCTACCTGGATCAAGTGATGTCTACAGAGT
AGGGCAGTAGCTTCATTGAACTCATTCAACAAGCATTATTCACTGAG
AGCCTTGTATTTTTTCAGGCATAGTGCCAACAGCAGTGTGGACAGTGGTGC
ATCAAAGCCTCTAGTCTCATAGAAGCTTAGTCTTCTGGAGGATATGGAAAA
CAGACAACCCAAACAACCAACAAAAGAGCAAGATGCTGCAAAAAAAAAAA
AAATGAATAGGGTGCTAAGATAGAGAAAAGTGGGAGAGTGCTATTTAGAC
AAAGTGGTAAAAACAAAGCCCCCTTGTGAGATGAGAGCTGCCGACAGGAGG
GGGCGGGTCATGGTTGTGGGTTTTTGGGTAGGACATTCAGAGGAGGGGGC
GGGTCGTGGTTGTGGGTTTTTGGGTAGGACATTCAGAGGAGGGGGCGGGT
CGTGGTTGTGGGTTTTTGGGTAGGACATTCAGAGGAGGGGGCGGGTCGTG
GTTGTGGGTTTTTGGGACATTCAAAAGAGTCTGAATGCACCCAGGCCTAC
AACTTCAAGATGGTAAAGGACAGCTCCAAGGATCAGAAGAAGCATGCTTG
GAACTGGGGCATTTTGAGAAGGAGGAAAAATATGCAGAGACTAGTGCTTG
CAGAGCTTGCATGTGGATTTTCAATTTGAGGTACAATGAAAACCEATTAATG
GGTTTCACACAGTGCAATGGCCTGACCTCACTTATATTTCTTAAATAGA
AAACAGATCAGAAGGAAGGCAATAGAGAAGCAGAAAGTCCAATGAGGAGG
TTTCACAGCAGTCATGGGGGTGGGGTAAGGAAAAGAAGTGGAAAGAAACA
GACAGAATTGGGTATATTTTTGGAGATAGAACCAACAGAAGGAAGAGGAG
AAACAACATTTACTGAGAAGGGGAAAAAGTAGGAGAGGAATAGGTTTGGGA
AATAAATCCTGCTGACATTGGAAACCCCAAGGAAGCCTCAAAAGTATATT
TACTTGCTTTAGATTTAAAGAATAGGAAAGAAGCATCTCAACTTGGAAAT
TTGAAATCTATTTTTCCATAAAAGTATTGTTAAATTCTACTCATACTCAC
AAGAAAAGTACATTCTAAAGAGTATATTGAAAGAGTTTACTGATATACTT
AGGAATTTTGTGTGTATGTGTGTGTGTGTATGCGTGTGTGTGTGTTAAC
CTTCAATTGTTGACTTAAATACTGAGATAAATGTCATCTAAATGCTAAAT
TGATTTCCCAAAGGTATGATTTGTTCACTTGGAGATCAAAATGTTTAGGG
GGCTTAGAATCACTGTAGTGCTCAGATTTGATGCAAAATGTCTTAGGCCT
ATGTTGAAGGCAGGACAGAAACAATGTTTCCCTCCTACCTGCCTGGATAC
AGTAAGATACTAGTGTCACTGACAATCTTCATAACTAATTTAGATCTCTC
TCCAATCAACTAAGGAAATCAACTCTTATTAATAGACTGGGCCACACATC
TACTAGGCATGTAATAAATGCTTGCTGAATGAACAAATGAATGAAGAGCC
TATAGCATCATGTTACAGCCATAGTCCTAAAGTGCTGTTTCTCATGAAGG
CCAAATGCTAAGGGATTGAGCTTCAGTCCTTTTTCTAACATCTTGTTCTC
TAACAGAATTCTCTTCTTTTCTTCATAGGAGATGCCTGAGATACCCAAAA
CCATCACAGGTAGTGAGACCAACCTCCTCTTCTTCTGGGAAACTCACGGC
ACTAAGAACTATTTACATCAGTTGCCCATCCAACTTGTTTATTGCCAC
AAAGCAAGACTACTGGGTGTGCTTGGCAGGGGGGCCACCTCTATCACTG
ACTTTCAGATACTGGAAAACAGGCGTAGGTCTGGAGTCTCACTTGTCTC
ACTTGTGCAGTGTTGACAGTTCATATGTACCATGTACATGAAGAAGCTAA
ATCCTTTACTGTTAGTCATTTGCTGAGCATGTANTGAGCCTTGTAATTCT
AAATGAATGTTTACACTCTTTGTAAGAGTGGAACCAACACTAACATATAA
TGTTGTTATTTAAAGAACCCCTATATTTTGCATAGTACCAATCATTTTA
ATTATTATTCTTCATAACAATTTTAGGAGGACCAGAGCTACTGACTATGG
CTACCAAAAAGACTCTACCCATATTACAGATGGGCAAATTAAGGCATAAG
AAAATAAGAAATATGCACAATAGCAGTTGAAACAAGAAGCCACAGACCT
AGGATTTTCATGATTTCAATTTCAACTGTTTGCCTTCTACTTTTAAGTTGCT
GATGAACTCTTAATCAAATAGCATAAGTTTCTGGGACCTCAGTTTTATCA
TTTTCAAATGGAGGGAATAATACCTAAGCCTTCTGCGCAACAGTTTTT
TTATGCTAATCAGGGAGGTCATTTTGGTAAATACTTCTTGAAGCCGAGC
CTCAAGATGAAGGCAAAGCACGAAATGTTATTTTTTTAATTATTATTATA
TATGTATTTATAAATATATTTAAGATAATTATAATACTATATTTATGG
GAACCCCTTCATCCTCTGAGTGTGACCAGGCATCCTCCACAATAGCAGAC
AGTGTCTTCTGGGATAAGTAAGTTTGATTTCAATTAATACAGGGCATTTTG
GTCCAAGTTGTGCTTATCCCATAGCCAGGAACTCTGCATTCTAGTACTT
GGGAGACCTGTAATCATATAATAAATGTACATTAATTACCTTGAGCCAGT
AATTGGTCCGATCTTTGACTCTTTTGCCATTAACTTACCTGGGCATTCT
TGTTTCATTCAATCCACCTGCAATCAAGTCCTACAAGCTAAAATTAGAT
GAACTCAACTTTGACAACCATGAGACCACTGTTATCAAACTTTCTTTTC

FIG. 3 (17 of 52)

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TGGAATGTAATCAATG1 . FCTTCTAGGTTCTAAAAATTGTGATCAGACCA
TAATGTTACATTATTATCAACAATAGTGATTGATAGAGTGTTATCAGTCA
TAACTAAATAAAGCTTGCAACAAAATTCTCTGACACATAGTTATTCATTG
CCTTAATCATTATTTTACTGTCATGGTAATTAGGGACAAATGGTAAATGTT
TACATAAATAATTGTATTTAGTGTTACTTTATAAAATCAAACCAAGATTT
TATATTTTTTTCTCCTCTTTGTTAGCTGCCAGTATGCATAAATGGCATT
AGAATGATAATATTTCCGGGTTCACTTAAAGCTCACATTACACATACACA
AAACATGTGTTCCCATCTTTATACAACTCACACATACAGAGCTACATTA
AAAACAATAATAGGCCAGGCACGGTGGCTCAGACCTGTAATCCCAGCAC
TTTGGGAGGCCAAGGTGGGAAGATCACTTGAGGTCAGGAGTTCAAGACCA
GCCTAGGCAACATAGTGAGATCTCATCTCTACAAAAAATAATGAAAAAT
TAAAAAATGAGCTGGACATGGTAGTACACACCTGTAGTCCCAGCTACTCG
GGAGGCTTGAGGTGGGAGGATCACTTGAGCCTGGGAGATGGAGGCTGCAG
TGAGCCATAATCACACCATTGCACCCCAACCTGGGCAACAGAGTGAGACC
CAGTCTCAAAAGATAAATTTTTAAAAATGTTAAAAAATATATAAAAGAGA
ATTTTAAAGAACAATAATAGATCAAAGCATGGATGCAAGATATATTTA
GTTGGAAAATCAAGGTTAAAAATCAAGGGATCTTGGAATTAGGTGTGGTAG
ATTTGGGTAAGGAGTAGTCTAAGATGACCCTGTTTCTTGGTACTGGAGAC
TGGATGAGTGGCAGCGTCTTAACCATATTTTTGGTAGAAATATGGAGGTC
TTCTCCATTCCAGGATGAATGATGAGTAAAATTTTAGGCATGTAATTTGA
GCTACTAGAAGGACACTCAATTGCAGATGTACAATGGGGAGATGATAACC
TATCTGGAACCTCAGAAAAATAACTGTATATAGATATGAAAGACATCAGTA
GGTATGTAGTAGATAAAATCCTAAAAGTGATGTCAAAGGGAGAAGAGAAG
TATATGGTGAACACTGTTGTTTGTCCATGCAATTGCCATCTCTTCTTCTT
CCTTACTGACAGAACCCTGATTTCACTGAGAAGTCAACATGCCCTTCCCC
AATTGATGAATCCAATTGGTTGAAGATTATGTTCAATTCTATTCTTACATG
ACTAAGTCACGTTGACTTAATCCTATCAAATGAGATGTCGATCTGGAAAC
AACTTCTGGAAAAGATTTTCTACCTTGATAAAATAAAGAGCCATATAGAT
GGTCCTTTATCTTCTTCTTCTTCTTGAATGAGATATGTTCTATGAGGAAGT
GAAGCTTAGAACTGTGGTCAGCAACTTGCAACGACTGGGAAGTCAGAGCC
ACACAATGAAGAATGCAGAGTGGAAGGAGAAAAAGAGCCAGCATCTCTGA
CAACATTGTTACACCGAGAACCTACCTCCAGATTTTAAGAAAACAAGAAA
TGCTACTGTTATTAAGCCATTTCACTGGGTTTGCTATGACTTGCAGTCAA
ATCTAGCTTAACTGATACAGAGCACCACAGAGAACTGGTCTCTCATTTGT
CTCATCCTGTTCTTTCTAGCAGCCACGACTTTCCTAGGGTTTCCTTAGCC
CAAGTCTGGCTAGAGCAAGACTAAGTAAGACTTGATTCCTTAATGTCCTT
TTGTTTTAAGAAATATTAAGAATTATTTTTATATTAATATATTTTAAGA
AATAAGGAAATACAAAACACTGAGCAAGCAACACAAATTCAAGAAATCTT
AAAAAGTATAATAGCTGCTCAGTCTCTGATTAACAGTGAAATATGGAATC
ATTGTAGAAATGGCCTTGAGCGTTATTCTCCAGGCCAGCTATCCTTAT
GGTCTGCCCCACCTCCCTCATTGCCTAAACAGTAAGAGAGTCCCATGGTG
AGACTCAACAGTCTTAGCACAGAACTTGTTACAGTCTATTTCTTTTCTTA
CAGTCTTATATATCAATTCCAAATCAATGAGAGTAAAGCCCAATCCCTGC
CTTTAAACCCAAAGGACAGAAGCCCAAGCCCAAGATATTCCCTAACCT
TCTCCCCCT

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CCTGTCGCTCCCTATGTTTAAAGCTGGGGATCTCTTTTTCTGTGTCTAA
TTATTTTCTTCATTGGCTTGAAAAATCTGATAAAACATTTTAGGACTGTG
TATAAAATAGAATTAGCCAAGTGCAATGTCTTTATTCAGAAGAAATTTCA
TGGACGTTGTGCCTACTCTCTTGGCTTCTGGCTTCATGGCTTTCCAGAT
CCCACAGTAAGCTCTGGATAGTAGAAGTTATAGTAAGACTGACTTCTAAA
TAAATGAAGTGACTTTAACCTTACTGATATGGCTTAAAGAAAAGGAGTGG
CCTTTAAGATCCATGAACTTCTCAAACAAAAGTGATAACGTTATCTCCAT
GCATATATAATACTAAATATAATGCAACTGAGAGAAGTAGGCTGTGGTAA
GAAAGGAGACCCAAGTGCCATCTGAAGGCAGCACTTACCACTCTGCTTCA
TCCCACCGAGGAAACAAAGCATGAGTATTGCCAGATTTTCTTCTGTTTCA
AGAAAAGCCAGAAATCCAGGTTTTTTCGCTGAAATGTCCTGATTTTAAATGT
TGGGAACATAATTTATATTTTGAATAACATTGTGTGGGACAAGTGAACCT
GTATGTGGAACCTGCTTTCTCCAGTGGCGACCAGTTTGGACCGTTGATAC
TCAGCAAGTTCAGCCAAGTGCGCCTTGTCATTGTCAGTCATCAAGGTGAT

GTGTGATTGGTCAAACAATTAGTTTTGCTCAGCATCTCGTGTGTTTTCAA
AGGACCTGAGGGTTCATTTGCCCATGCAGATCTTGTAGTCCTGTTTATTC
TATTAATTTATCTTGCAAATCTATAATGTTTTATTTTAAGCAGCGAGAGC
CGTGGCAGCCTTTGGTCTGGACCCTTTCTAATGATCATTTAGTATCAGGC
TATGTGGGAGTTGATTGTTTTGCATTGCCTGAAAGCCAACAGTATCACTC
CTCCTCTAGGTGTGGCAGAGATGTGAGAGAGGGAGACTGACAGTCTGTGG
GTGTGTATGCAGTGTTGGGGGAAGCGAGGCACAGGGGACAATACTGTGGT
GTATAAACTAGTCTAAGGTAGCATCAGGAAGTTCATGAAGCCAAAATGA
TTTTTCATAACAGCACAAAGACATTATTTGTTTTTGCCTCCCTCTCATTTTT
TTTTTTTTTTTGAGACAGAGTCTTGCTCTGTCATCCATGCTCGTGTGCAGT
GGTGCAATCTCGGCTCACTGCAACCTCCACCTCCAGGGTTCAAGCAATTC
TCATGCCTCAGCCTCCTGAGTAGCTGATTACAGGTCTGCACCACCCCGCC
GGCTAGTTTTTTGTATTTTTAGTAGAGATGGGGTTTTGTAATGTTGGCCAG
GCTGCCCTGTCATTTTTTTTTACTAGTGTCCAGTGGAGTTTTTTAGGGG
CTACATAACATGATACTGTCAATTAATCTAATGGCTAATGAAAGGGATATG
TATATGTTTTTTGTGTTTAAACAAACTTCTTTGGGGTCTCAATAATTTT
TAAGAGTATAAAGGGGTCCTGAGATCAAAGAGTTTGAGTTCTGCTGGACT
GGGACAGTGGTTGTCAACCCAGATTGTACATTAGGGTCATCTGGGAAGCT
TTAAAATAGTACTGATGCCCAACCTTACCGCAAACCAATTAAGCCAGAAT
CTCTGTGGATGAGAAGTCTTCATTGTCATCATCACCATGACCATCATCAT
TGTCACCGTCACTACACCATTATCATCATCATATCATCTTCATTATC
ATTGTTAGTATCTCCATCACCATCATCAGCATCACCATTATTATCATCAT
CATCATCCCCACCATCATCCTCATCGGAACCTTCACCTGCATGGAGGACAA
TCCACTATGCATTAGGTGCTATGCTATTTGCTATACTCCTTATTCTCACA
ACTGCCCAGAGAGGCTGATATTATCTCACTTTATAACAGGAGGAATCTGG
ATCGGAAAAGTTAAGGTAAGCTAATTCACAGAGCGAGAAGAGATAGAGCC
AGGATTCGAAACCAGTTCTCTGCTACATCAATGTTCCCAGTCCTTGCACT
ATTGAGAACCTCTTTAGTTATGCTTTCACCCCTCCAACACCACAGTAAAT
TTTTTCTTTTTTTTAAAAAAATTATACTTTAAGTTATAGGGTATATGTGCA
TAATGTGCAGGTTTGTACATATGTATACATGTGCCATGTTGGTGTGCTG
CACTCATTAACCTCGTCATTTACATTAGGTATATCTTCTAATGCTATCCCT
CCCCGCTCTCCCCACCCCATGACAGGCCCTGGTGTGTGATGTTCCCCACC
CTGTGTCCAAGTGTTCTCATTGTTTCAGTTCCACCTATGAGTGAGAACAT
GTGGTGTTTGGTTTTCTGTCCTTGTGATAGTTTGCTCAGAATGATGGTTT
CCAGCTTCATCCACGTCCCTACAAAGGATATGAACTCATCCTTTTTTTATG
GCTGCATAGTATTCCATGGTGTATGTGTGCCACATTTTCTTAATCCAGTC
TATCATTGCTGGACATTTGGGTTGGTTCCAAGTCTTGCTATTGTGAATA
GTGCCACAGTGAACATTCATGTGCATGTGTCTTTATAGCAGCATGATTTA
TAATCCTTTGGGTATATACCCAGTAATGGGATGGCTGGGTCAAATGGTAT
TTCTAGTTCTAGATCCTTGAGGAATTGCCACACTGTCTACCACAATGGTT
GAATTAGTTTATAGCCCCACCAACAGTGTAAGCAATTCCTATTTCTCCA
CATCCTCTCCAGCACCTGTTGTTTCGTGACTTTTTTAGTGATTGCCATTCT
AACTGGCACCACAGTAAATTTTTATAGATTTTATAAGCAAATTGTATTTA
CTGTGCAAGAATTGGTTTATTTTTTAAACCATGTGTTGCAAACATAACAAT
GGTTAATTGTGATATTTGCTCAGTACAAGATCATCAGATCACTACACAGA
CTTGAGGTAATTCCACCTAAAAGCAAAGAGAACTGACCCACATTAAGT
AGAAGTCTTTACTTATTTATTTCCCTATAAACGAGCCAATATGAAGAGAAG
GCCTTAATGTGGTTAACTATGTAATTTTTTTCTGACTTTTTTGAAATACTG
AGAAGAGCTCATGACTCTCCCATCTCCTAATTCTACCTTGGTGGATTTTA
GACTGACCACAACCTCATGGGTAAATGAGGGAAGACGAATAAGAAACCTTG
CTTTTTTTTCTCCTTGTTTTTGGCTGGCTGCAGTGGCTCACACCTGTAA
TCTCATCACTTTGGGAGGCCAAGGTGGGAAGATCACTTGAGCTCAGGATT
TCAAAACTGGCCTGGGCAACATAGTGAGACCCCATCTCTAAAAA
AAAAAAGGCGACAGGCGGTGCGTGCCTGTAATCCTACCTACTC
AAGAAGCCGAGGTGGAAAGATCACTTGAGCATGGGAGGTCAAAGCTGCAG
TGAACCTTGATTGCACCACTTCATTCCAGCCTGGGTGACAAAGCAGGACG
CTGCCTCAAGAAAACAAAACAAACCTTAATTTTTTGGCTATTCTTTTC
TGGTAAGAATGGTATAGAGATGGGGATGAGGATGGCTATTGTATGAGAGA
GCAAACAGGGTCCAAGCAGTGCTCTGGGCTGTCTAAGGACCAGTAGTCAG
CTTAACCTCTCAAATTTCCAGGGAAGGAGTTCGGAGTGGTAGAATATCCT

FIG. 3 (19 of 52)

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GGGTATGCCCAAAGCATLACCTTGCAAATAGCCTGTGATGAATAATTTG
TTCAATTTGTTATGACTGGAACTGGCTTTGTGTATGCCAGAGAATGGGGG
CAGGAAAGAGAGATTGGTGTCTTGAGCTCTCTGTGCCTCTGGGGCAGTGA
TGCTTTTCTCTCATGTGGAAGGAGAGCATGACTGAAAAGGTGCACAAAT
AAGGTGTCTGTGAGAGAAATTAACCTTCCAGATACAGAGACACAACCTTC
CCCAAGAGGTCCTCATTGCTCTGCCTTTTTTCTCTTTTTTTTGCTTGTCT
AQCATTAAATAACAGAACTGATTATGACCTCAAAGAGAGGAGAAAGCGA
CTCTCCCCACCCTAGAGCTAGTTAACCACCATATCTTCCTAGATATCCTT
GAGAGCAATGTAACCC

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GTGAACTCGTTTTACCTGTGTAGCAGACCAAGCCGCAGACAAAATCCNTC
AGACACCAAATTAAGAAGGAAGGGCTTTATTGGGCCTGGAGCTGCGGCA
AGACTCACGTCTCCAACAACCGAGCTCCCCGAGTGTGCAATTCCTGTCCC
TTTTAAGGGCTCACAACCTCTAAGGCGGTCCACATGAGAGAGTCGTGATAG
ATTGAGCAAGCAGGGGGTATGTGACTGGGGGCTGCATGCACCTGTAGTTA
GAATGGAACAGAACATGACAGGGATCTTCACAGTGCTTTTCTTATGCAAA
TAACCGATTAGATCAGGGGTCGATCTTTACCAGGCCAGGGTGTGTCACC
GGGCTGTCTGCTTGTGGATTTCAATTTCTGCCTTTTAGTTATTACTTCTTT
CTTTGGAGGCAGAAATTGGGCATAAGACAATATGAGGGGTGGTCTCCTCT
CTTACCTGCGGGGAGTGAGCTCAAACCTCTTAAAGGAGTTACCTGCCTTC
CATCATCAGGGAAGCAGGAAATCTTGCTTCCTTGTTGGAAGCAAGTAAA
ACTCAAAACAAACAAAGAAAAAACAGGGAGTTGTACAGCAAAATAAACT
TTTGATTTTGACCAAATTTTGGGAGATCAGGAATTCCTCTGAAGGAGATGC
TTTCAGACCTCAGCAAATTGTCTGTTGGTTTGAGCCATAAAGTTAGCTC
ATGCTGGTACCAAACACCAGTAGGAGATTGTCAAAGGTAAGAGGCATCT
CCACTCAGAATCCCTTCGTGGTTACCAACATGTGAACCTTGGAAATCTGA
GACAGGTCTCAGTTAATTTAGAAAGTTTATTTTGCCACGGTTGAGGACAC
CCACCCATGACAGAGCATCAGGAGGTCCTGACCACATGTGCTCAGGGTGG
TCTGAGCACAGCTTGGTTTTACACATTTTAGGGAGACATGAGACATCAGT
GAATATATGTAAGATGTACACTGGTTCCCTCCAGAAAGGCAGAACAACTT
GAAGCAGGGAGGGAGCTTCCAGGTCACAGGTAGGTGAGAGACAAACAATT
GCATTCTTCTGAGTGTCTGATTAGCCTTTCCAAAGGAGGCAATCAGATAT
GCATTTATCACAGTGAGCAGAGGGGTGACTTTGAATAGAATGGGAGGCAG
GTTTGCCCTAAGCAGTTCCCACTTACTTTTCCCTTTAGCTTAGTGATT
TGGAGGCCCCAAGATTTATTTTCTTCTACATCACTGTGGGCAGCTGACT
AGGAAAGCTTTGTAGGACTGGTGGGCAGTGTGAGAGCCCAGTGGGGGGTG
GTGGTCCTGTGCCAATGGTAGCAACCACCTGTGAGGCTGAGTAACTCAT
TTCCCAACCTCCTCTAGCAGCCCCAGTGGAGATACAGAGGAAGCAGACTA
GCGATACAACCCAGCCTGAAGTTTTGTCTGGTGAGTGTAATGGAATAAAA
ATGGGAAGGGTGCTGAAGAGACCAGCAAGAAAATGGTTGAAGAGATGGGG
CACAGAAATTAAGCTGGATCAAAAAGGACGGAAAAGCAGAAAGGGCCGAT
AGAGAGAGGGGATATCTATGGGTTCTGCGATTCTGAAAAGGACAAATCACT
GGTGCTTTGAGAAGAGAGAGGGGTGAGAAAGCAGGAAGGCTGGAGGCTGTC
ATCCAAGAGGCGGACATCTGTGAACATGATTCCAAGAGTCACCAGACCAT
GGGGGTGGCCAAAGGGAGTGCTCTTCTCACTCCTACTCTTAATTCCTT
GTACTCAAGATAATAAGTTCCCAGAAGAGAAGTACCCATATTTAATTCAT
CTGTGTCTTCTTAGCAGTACTAAAAATATTATATGAAAGGTATCAAACCT
TTGAGAATGTGTGCTGCTAAATTGTTAAGGATGCTGGAAAACCTCAAGACG
TCCCTGATCCTGAGCCTGAGTATGAGCCTGTGGTGAGCCCAATGCAGGTC
TCCATTCAAGACAAAGGCCTCAGGGAACGGATGAGACCTAGGGACAGAGAT
GCATGCTGGAGCAGCATTCCTCATCCCTACTGCAGCTCAGGCCAGCTGAC
TGCTTTATGAGTAAACGTTACCAGGGAACACTTTGCAGTCTTAACACACA
TGCCACCTGTGACCACTGATCCCTGTTGGGTGACCACTGACATCAGAGA
TTCGATGGCAGCAATGAAGACAAGGCTATCCTCATTAGGAAGGAAGGAA
GGAGGAGGGAGGAGGGCAAACGAATCTTTCCTGCTTGTCAACCACGTCCA
TCTCTGTTAGGTGATTTCCCATGTGTGACTTTGTTTATCTTTATAATAAC
TCTGAGAGGTAGGTCTTGATGTCCACATTTTGAACATGAGGACATCCAGC
CAGGAAGTTGAGTTCTGGGGACATAGCTGAGAGGGCAAAGCTACATATAA
ACCCCTCTTTGTTTTTTCTGGCTTATCCACTGAGTGCCCCCTGCAATCCA
CCAGCCCATTTGTGAAGTGCACTACTATAGGTAAGTTGGCACAGGAGGAGT

GGATGTGGGCGATTTTG. CACAGCTCTCCAGGAACCTTACACACTGGTGAG
GAGGGCCAGGTATGTTCCCTGACCAGTCACAATCAAAGCAACCTCCTACTA
ATCAGGGAGGCTTGGTACCTGGGGAATGCTATGTTGAAAGGTTCTTTTCT
GGGTTTTAAATGATGGGTCTATTTCCCTTATTCTTAAGATTGCTTTTTTT
CTGGCTAGAACTTAAAAGAAATTTTCAGTAAATTTCCCTTCCCTGGCAC
AAAGTGAGCTTGAAATGAATTCCTCAGGTGGCCTTGATACTTTAAATATT
GCCTCCTATAAAATCAACCTTTAGAAGAAGGAAGTCAAAGAACATGCTAG
ATTTACAAAGGTTAATTCCTTGAAATCCAGTTATCTACAGGACAATGTT
GTCAAAGAAAAAATTATTTGGCCAGGCACGGCGGCTCATGCCTATAATCC
CAGCACTTTGGGAGGCTGAGGCAGGTGATCACCTGAGGTCAGGAGTTCGA
GACCAGCCTGGCCAACATGGTGAAACCCCATCTCTACTAAAAATACAAAA
AAAATTAGCCAGGTGTGGTGGTGGGCACCTGTAATCCCAGCTACACGGGA
GGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGAGGAAGTTGCAGTGAG
CCAAGTTCAAGCCACTGCACCCAGCCTGGGCAACAGAGCAAGACTTTGT
CTCCAAAAAATAAATTTCAATGATATTTTTTAAATTTCATGGTAAGGAA
GATTTTCATTGAGAACCAGCACAGAAGATATAGGAAACACTGCAATGGGAC
TTTGCGGTGGGGGAGAGAGATTGAACACAACCTACATATACAGCACGGGCA
AGGACATATTCATAGCCAGGAAGCAGAGCAAAGATCAGTGGATGCGAAAT
TACTAAGAGGAAACATGAAAAATAAGGGAGCTTCTGCCTAAACCCACCTA
ACCGGATCCTTGCTGAAGACAGGACAGGGTGATTGGACACCACTTTGGGG
ATGGTGGAGGATGGGGAATCCAGTGAGATTTCAAGGGTGATGCGATATTG
AACATACAAAGTTCTTGCTAAAAAAGGATTTTACAAGAAAGTGTAACAAT
GTGCCTGGGACAAGGTGCAGGAGCCCGACGGAGATGTGGTCCAGCAGAGA
ATATGTGCCGAGATGATAGGTGAGTTCTCTGACGAAGGATATATGCTGAT
CCAGCCAGGGTGAAATGCTCAGAGAAAGCACGGAGGGGCTATGTCCGTTG
CCCCAGTCTCCACGCGGTCAAATCTGATCCCGTTGTGAGTGTGGCCGTTT
GTAGAAAGCAATCAGGGGGGGTCCCTCCCC

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AATATATATTTTTTATANNATNTGAGACAGGTTCTCACTAGGTTGCCCAG
GCTGGTCTTGAATTCCTGCCTTCAAGTGACTCTCCACCTTAGCCTACTG
CATAGCTGGGATTACAGGCACAAACCACTGCATGCAGCTAACTTTGCTTC
TCATTCCAGCACTTTTTATTCCACTGATTATATGTATATGTATATCTGCA
TCATCTCTCTCTCTCTCTCTCTCTCTCTCTCTATATATATATATATAT
ATGGAAATATCTCTCTCTCTCTCTATATATATATATATGGAAATATATATCT
CAGTCTCTCCTATCCTCCTTTAATCAGTTTTGCTATCCTGTCAATTCCCC
CAACGAGTGTGATGTTGTGAAATATATATTTGTTCTTCATCTCCTGTTTC
CTGACATACAGCTTTTAAAAACCCCTTGAATCTCTGGAATAATAAGAGTG
TCTTTTGCATGCTAATAGATGACTGCTGGCTGGCAGCCCCAATGCAGTAG
CTTCATGATGGGGTTTGTACAGGAAAGACCAAGGCAGGATTGGAGACTT
GAGACTGTTAGCCCCACTCCCCAACCACTGGAGGGAGTGGAGGGGCTGAA
GGTTGTGTGAGTCACCAATGGCCAATGGTTCGGTCAATCATGTGTATGTA
ATAAAGCCACTCTTAAAAACCCAAAAAGGACAGGGTTTGAAGGGCTCCC
AGATAGCTGGACACATGAAGGTTCTTGAGGGTGGTGCCCCAGAGGGGCA
TGGAAGCTCCACACCCCTTCTCACATGCTTTGCTCTGCGCATCTCTTCAT
CTGGTGTTCATCTGTATCCTTTGTAATATCTTTTAGAATAAACTGGTAAA
CTTAAGTGTTTTCTGAGTTCTGTGAGCTGCTCTAGCAAATTCACGGAAC
CCGAGGGAAGCAAACCCAGATTTATAGCCATCAGTCAGAAGCATAGGTGA
CAACCTACCACTTGTAACCTGGCACCTGAAGTGGGAGGCAGTCTTGTGAGA
CTGAGCCCTCAACCTGTGGGATCTAACGCTAACTCCAGGTAGATAGTGTT
GGAGTGAATTAGGACACCCAACTGGTGTGCGCTGCTGGAGGACTAGTGGT
GGGAGAAATCCCAAGCATTTCCGGTGACTAGAGGTCACAGAAGAACTCAG
TGTTGAGGTGTTGTGACAGTATGGTAGGGAAAACCTGCGTCTGGTTTTTTC
CTTTTACAATCAGTTAAATATTTAACACAAGTCTACTGTATATTAGTAAA
AGGGTTACATTTTTTAATGTCTTGACAGTTGCACTTTGACAACTTCCATA
TCAATCACTTTTTTTCGTGTCCGTTTGGAAACCAAAATCACTTGGGATACC
ATGAACCAGGCTGCAGCGTATTCCTCAGGCCTTGAAAGCTTGGAGGCCAT
TTTGCCAGCCNTAATCCCTGTGAATACCAGGCTTCGTGGATTTAAAAAAT
AGACTTGAGGCCAGGCCTGGTGGCTCACACCTGTAAGCCCAGCACTTTGG
GAGGCAGAGGCGGATAGATCACAAGGTTAGGAGTTTCGAGACCAGCGTGGC
CAACATGGTGAAACCCCGTCTCTACTAAATATACAAAAAATAATTAGCCG

GGCGTGATGTTACACG CAGTAGTGCCAGATACTCAGGAGGCTGAGG CAG
GAGAAATACTTGAACCTGGGAGGCAGAGGTTGAAATGAGTCAAGATCGTG
CCACTGCACTCCAGCTTGGGCGACAGAGTGAGACTCAGTTTTTCAGGGGAG
TTAAAACAATACAAAAAAGAAAAAGACTTGAACAATGAGGCTCCACTGG
ATGGATTTAGGGGAATTACAGGAAGCAGGACCTGACGGTGCAATGCCACA
CTCCACCTGTCCAGAATTGGACCTCACCAAGGGAGGTCTGTGGGGACAGG
GAGAGGCCCTCTGCCTCCACCCCTCCTCTACTCCCCAAACCTGAGTCA
GGCTGAATGTAGTAAACCTGGAACAGAAAAGTT CAGTTTGGCAATAGGTA
TCTGAAGGACTCCAGGTGCTTCTCCCTTGATTCAAAATTTTACTTATAAA
AAAAATTATAAGAAAATTCTACTTAAAAGAAATAATCAGGGAGGTACAAC
AAATTGTACTTTTTTTTTTTTTTTTTTTTTTTTTTTTGAATGGAGTCTCACTG
TTGCCCATGCTGGAGTACAGTAGTGTGATCTCGGCTCACTGCAACCTCCG
CCTCCTAGGTTCAAGTGATTTTCTACTTCAGCCTCCCAAGTAGCTGCGA
TTACAGGTGTGTGCCACCACACCCGGCTAATTTTTTGTAATTTTTTGGTAGAG
ACGGGGTTTCACCATGTTAACCAAGATGGTCTCGAACTCCTGACCTCAGG
TGACCCACCTGCCTCAGACTCCCAAAGTGTTGGGATTACAGGGGTGAGCC
ACTAAGCCCAGCCATTGTACATATTTTGTGGGTATTTACTAAAACATTAT
TCAAAATAGTAAAAAAAATTGAAATAAACTGGGGACTGGTTAAATAATT
TTGGGTACAACCACATGATGGAATACTATACAGCCATTAAAAATTACATT
GAGGCCAGGTGTGGTGGCTCATGCTTGTAATCTTAGCACTTTGGGAGGCC
AAAGTGGGAGGATTGCTTGGAACCCAGGAGCTCAAGACCAGCTTGGGCAAT
GTGGCAAAACCTGTCTCTAAAAAAAATACAAAAAAATTAAAAAGCT
GGGTGTGGAGGCACACACCTCTAGTCCCAGCTACTCAAAGGGCTAAGGTG
GGAAGATCACTTGAACCGGGGAGGTCAAGGCTGCAGTGACCCAAAATCGG
GTCATTGCACTCCAGCCTGGGCAACAAAGCAAGACCCTGTCTCAAAAAAA
AAAAAAATACATTGAAGAATATCTTACGGTATGGATAAATATTCATTTTA
CAGTGATAGATGCAAATAAAAGCAAATTACAAAATATACAGTTTAATTCC
AACTTTGATACTACATATGTATATATGAATACATGCATATGTTATGTATG
TATATGTAAATATAACAATATATGTTCTATATATGGATATTATATATTTA
CACATACATACACACATATATAATATCTTCTCTAGAGAGCAGAAAGAGAG
TAGACAGATAATGAAGATAGGATACAACTCCAGTCCAGCTCAACCTAGGG
GACTTGTTTTAAAGCCTCAGGAGAGAGAAGTTGGGACTAGAAAGCAAGGC
AGCTATTTGTAAAGCATCTTTGTGTTTCATGCTATTGGGGTGGGAAACAAC
AGCACAACTTTTGAAAGCCCCCTTTCTACTCACCCACAACTGCAGAGCA
GCTTTAGGACCCTCAGAGTTCAAGAAGACCATTTGCAGAGTAGAAGAAGT
AAAAACATGTATGAACTTGACCTGAGCTCATGGACTGTGCCATGAGGGA
AATTCCTAAACAGCAGGAGAGGCCCTGGAGGAAGGCAGAGGCCCTGCAT
CAGCAAGTCCAGGCAAAAGCCTGCATTCCATAGATGCTCATCTCTCTGGC
TGGTGAGGTCTAAAGACGTTTGGTCTCAATATTAAGTCTCGTGAGAGAGG
TCACAAACCCAGTCCCTTGGCCACAAAAGGAAATAAATTCTGGCTTGAGA
CATTAGGGAGGAACAGGGCAAGGGGAGGTTCAAGAAAGTTTTAATGGATG
AGATGATATTTAAGCAAGGCCCTGGAAAATGAGAATTTCAACCAATAGCC
ATATGGTAGGTCAGAAAGCAAAGATAAGGAGGGGGCAAGTGCAAGGGGCA
ACATCAGATATGACCAGGGTGTCTGGGGGCATGGCTGATGGAGAAGAAGA
TTAGACTGGAGTTTGGGAATGCCACAGTATCGAGGTTGGATTTAATCCTA
TGGGTAATAAAGCCAACTGTTCAACCCCCCAACCACTTGCAATATGGCTC
CAAAATAGCAGGTGTTTGATAAAATGACTACTTTTACTCTACTATTCCCT
CCCTCTTAAGAAGAAAAAGAAAGTGGAGGCTCAGAGAAAGGCAGTGGCTT
GTCCCAATCACACTATGATTTGGCCACAAAACAAGAACGAAATGTTACAC
CCAAAAATGCTGCCTCCACCTCCCTTCCTTGCTTTCCTCCCTGCTGGACT
ACAGACTATCTCAAGAGTGACGTACACCATCAGGGCTTCAGCTTTTCCCC
GAAACAATGCCAAAATATTAGCCATACGTCACTGTAGTAAGAGCCCTGAA
TTGGGAATCCCAGCTTTGACGCAGACATGCTGATTGACTCTGTGACCATT
CTCTTCACTTCTCCACTCTATTCTTCCCCACCTGTAAAGTGAGGTCCTTT
CCAGTTATAAAAAACAGATGATGCTATTGTCTGTTTTGTATCTAATCTTG
CTGTGTTATAAAAAAAAATAAGGCTCTGTACATTCATCTTGGCCAATTC
CCTTCTTATCTCTACTTCCCACAGCCCCTTTTTCTACAGAAAACCAGCAT
TGTTCTTCTGGATCCATCTCTTAAGAAAGCGCTTTGCCTCCCCGGTTATT
TAGGTGATAAGAAGTGTCTTAGATGACAGCCCTGGAATGGGCTGGAGGCA
ACAAAAAAGCAAGTGAAATAGACAGTTACAGCGACGACAATAATAACAAC

FIG. 3 (22 of 52)

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CAACACCTCTCACTAAAGAGAAAGAAATAAAAAAGAAAATTAAAATCTGC
CGCAATGCCACACAGTCATTGAATAACTGCATGTGTACAGCACTTGGTT
ACTTTTACATACTTCATATTTTAGCCTTCATAGCAGCTCACAGGGGTGGA
TTTAATTTTGTAGTCCAACCTCCTGTACGGTGCCTGGCACAAGTATAATAA
ATGTTCTGTGAATAAATGACCCCTCTTTTGTAGATGAGGAAATCGAGGCTCA
AGGAGAACAAGCAATGTAATGTCCCCCTCCTGTTGAGCCATCTGCCTTTC
ACGCCACTGAATGCAGTAGTCCTCAGTGCCCTGAACTTGACCCCTCTTCTG
CTTTTCGGACTGGTCCTTCTAATCCCGTTGTGACTCACTACACCACCTCT
CCTGCATATGACATCTACATTTTAAAACAAACCGTATGGAAATAACACAT
TAGTCGGCTTGTTCCTCCACCCCGCAAAAAAAGGCCTCTTTATAACA
GAAACTTCTCAGGCTGGTAGGGGAATTTTATTCCCCCATTTATGGTAGAA
AGGCCCTAACCTTGGACCTCACGCCATAGCTATTACATGGGGGAATGAT
GAATAACATGGGGAGCAGCATGTAAATATCATTGAGCCGTAGTCCAGACC
TATAACACATC

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GGGGGAGCTGCATGTGCCTGTGCGAGATCTGGGGGAGGAACAGGAAGATCA
AGAGTTCTGTGTAGGACATGTTAAGTTGAAGGTGCTTACAGGATAGCCAG
ATGAAGCATCAGGTGTGCAGTCAAAGATATGAGTCTGGAGCAGCACATCC
TAAGTCACCTCCTGCACCAACACAGAACTTCCAGGCCACTCACTTGAGCT
CTCCCAAATAGTTTCCAAGTGTCAATTATGTTAATAACCTATGAGCTTGAA
CACCAGATTCAAACCCCACTGCATGGCTTTTAAAGACCATCTCAAGGGCT
TGACACTCCAGGGAGCCAACTAAAGATGCCTGGTCCTACCATCAACCTCC
ACCCCATTTTTTATAGAAAATGTTTCTACCTGTCCTAAGGCAGGGTCCTG
CCCCACTCCCAGGCCCTTTAGATCCCCAATATTCCTCCTCCCTGAACCA
AAACCCTCATCATCTTCCAGCATGGGTGGGGCCTCCATTCTTGCTTCTGC
TCCCTTGAGCAGAAGCAAGTTTCTCCCAACTTGACCTGATTCTCCTCCTA
AGTACCAGTCACTGCTTTGTTTCTGGAATGAGAGAAAAAGACAGAGTGAG
AGAGACAATCCAGAACTCTTGCTCACTCACAGCTAGGCTGGGCATCTGGG
AGGATGGCTGTGTCCATGGGAACCTGGGAAAAGCCACACCCTTGGCACCC
TGGTCACCCACCTGTCTCCTTGGCAGATTCCGCACTGCTCTCTTGACCC
TCTACCAGGGCTAACCGGCTGCTCACTCTCCCAGCATGTCTTCCCACG
CCCACTCTCTAATTATTACATTCCCTTCACATAAACTGCCCTTCTCTCCC
AATCACCACATGTTCACTTCCCACCCAGCTGTCAAAGTCTGGCTCAACCT
CATTCCTGAAAAGGAAAAACAAACAAACAAACAAACAAACAAAGCAAAA
ACCTATGATGGATTAAGAACACACTTCATTCCAGGAACATGCTTATCTCC
TCTAACTCTCACAACAACACTACAGCAGGTAGGTGTTATCACACCCATCTCT
CAGGTGAGAAAACAGGCTCAACGAGTGCAGGAGGACACAGCAAGTCAGTG
ACAAAGCTTAAATTCAAGCCCAAGCCTGTTGGCAACCAACGTCTGTACCC
TTGATAGCTACCTCATTTACCACCAAATCCAGTGGCCTCAGGCCTGGCTG
CACACTGGGATCACCTGGTGCCAGACCACATCTTAGACCAGTCATACAG
AATCTCTTGGGCTGGGATCCTCCACGGTACATTTTAAGGGTCCCCAGGTG
AGTTCCACCATGGACCCAGAATTGAGGACCCAATACCGTATAACCATCTCC
TTCTTCATCTCTTCTAAGGCATCTCTTACTCGCTGTGCACTCCCATACCA
CTTTGTTCAATCATCCAATCATTCAATTGAGTCAGTTAGTCAGGAGC
TACTCACTAGTCCCCTGCCAGGTCTAGTCATGACATAGGGCTCTGGGGA
CCAACAAGAAGCAGGACCCATGCCTCCTGCTCTCATGGAGCTTGCTCTGC
AGCAGAGGAAGCAGTCAGTGAGATGTAGCAAATGTGAAATGTGCACAGAT
GGGAAAAGCAAACTTTAAAACCTTTAGGACAAAATACACAAGAAATCTT
TGCAACTTTGGGACAGGAAGGAACAACATTCCTTACACATGACACCAAAG
GAATCAACCATAAATAAAAAGGTGATCAATTTGACCTCATTTAAGTGTTA
AGCTTTTTTTCATTGAGAGACACCATTAAAAATTAAAAATACATGCCACAA
ACTGGGATACAATATTTACAACACTTATGTCTCACAAGGATTAGTTTTTC
AGAATATATAAAGAACTCCCGGCCGGGTATGGCCGCGCACGCTGGAATCT
CAGCACTTTGGGAGGCCAGCGGATCACATGAGGTGAGGAGTTCAAGACCA
GCCTGGCCAACATGGCAAACTCCGTCTCTACTAAAAATACAAAATTAG
CCAGGCATGGTGGCGGGCGCCTGTAATCCCAGCTACTCAGGAACTGAGG
CAGGAGAATCACTTGAGCCCAGAAAACAGAAGTTGCAGTGAGCTGAGCTC
ACATCACTGTAAGCCTCGGTGACAGAGTAAGACTGTCAAAAAAACGAAAA
CAAAAACAAAACCTCTACAAATAAATAAGAAAAAATAGCCCAGCAGGA
AAAAGTATATACATTTTATAAAGAATAAATACATTCTGTCAGTTTTCTA

ACATATATTTTTTAAGAGTAAATACAAATGGTTAGGAAACATTTTTTAAA
ATGCCCCAACCTCATTAATAATTATAGAAGTGAAAATTAAGCCACAATAAG
ATACGATTTTATACCAAATACAGTGTCAACACTTTGCAAGTCTGACCTCA
CCAAGTGTTACCAGACGTGTGCACTGACGTGGCTGCTGAGATACTGATGG
TGGGTCTGTAAATCTGTACTACAAACAATTGCAATAAAATGTAATAAATA
TACAATAGGTGGAGCAGGAAGTGACCTGCAACCATATAGCAGATAGGGCA
GGAAAAGCCTATGAAAGCTGACATCAAAGGGATAAGTTCCAGTTACCCA
GCTGAAGGGAAGGAGGGTGTTCAGATAGAGGAAGGATAAGCATGACCTA
TTCAAGGCCAGTGAAAGAAGCGTGCAACGGCCAAGTCAGGAGAACCTGAA
ATTGTGTCAAAGAGCTTGGATGCAAAGAGCCGTGGGAGACTATTGGGGGT
TTTAAGCAGGGATATAATATTCATTCAAGCATGCAGTAAAAGGTCACTGG
CACCTGCCATGGGCCAGGACTCGGGCTCTACATGATTGCGTCTGTTTTGG
AAATATCACCCCTGGCTGTGAGATGAAGAACAGGTAGGAGGGTCACAAAAC
TTGAAGCAGAGAGACTGTTGAGGAAGTAAGCTGTTTTTGTGTGGACTGTG
GCAATCACAGAGGCAGAGGATATAAATGCACAGAGACACAAGGCATGTGG
GAGGCAGAAGGAATCAAATACAATGAGTGATCAGATGTGGGGTTAGAGTG
GTGAGTGAGAAGACATACTCAAGGTGACACGCCAGGTATCTGGGTGGAT
GGTAAGACATTCATGGACTAGGATCGAGGAANGAGGTGGGGAATGGGACC
ATACCTGCAGTTTATAAGGGGTGGACGAGGGAAGATTATGCGGGAGACTG
AGAGAGGAATAGACAAAGGAATCCCGGTGCAGTATTACAGAACTGGGGT
GGGAGGGGGTGTANTTCAAAAAGGAAAGAAATTGTCAAATAGTATGAA
ATGCTGCAGAGAACTCACGGATTTTTTTTTTTAAGCTTAGAATTATTCAT
TGACTATGTGAATAAGAATAACTTTTATGAAAGAAGTTTTGCTTAAGTAG
TAGGAAGAAGCAAAATTGTTGAGGGCTGATGAGTGGGAGGAGAAGTAATT
GAAGGCACTCTTCAAGAGAAACAAAGCAGAAGGTGAGGAGAATACTAAT
GAAGGAGTTACGGCCTTCACTATTTTTGTTTTGCTTTAGATAAGCAAGACT
TGAGTGGGTCTGGTGAGGAGAAACAAGTAGAGTACAAAGTTAAAGGAGAG
ACAGACAGAGATAGAGATAGGGACAGAGAGAGAGACAGAGACAGAGCACA
AAAGAGCAAGGTCCCTGAGAACACGGGCCTTCTGTTTAAACCCAGCCAG
ATGTATTGCAATTCAATTCAGTACTAACCACCCAGAGTTTGTGTAGACT
CTACAAGTTAAAGAGCATGGTCCCCAACAAGACTGCTTCTACGTCAGATG
CCAGGCACACTTCAGGGGTCCCCAAGCCACTCATGTTTTTTGAATGACTG
CCATAAGTTCAAAAATTCCCACAATTCTCTCAGATTCAATAACTGGGTAT
AACCCTCATAGAACTCAAGAAAATGCTATCATTATTATTACAATTTTAT
TATAAAGGATACAAATCAGAAGGACTAGCCAAATGAGGAGACACATAGAG
AGAGGACTAGTAAAAAACAGAGCTTCTGCGTCCTACCTTCAAGGAATCAG
GATGCACCACCCTCCCAGCACATCAAGTGCTCATCAACCAGGAAGTTCCT
CTGAGCTCCAATGTCCAGAGATTTTAGGGAGGATTCATTACATAGGTATC
ATTGATTAAATCATTGGCCATGTACTTGAACCTCAATCTCCAGTGTCCCTC
TTCTCCCTAGAGGTCTGAAGGGTTGGCTAATATCATGTGGCTCAAAGCCC
CAACTCTAATTACCTTTTTTGGTCTTTTTCAGGGACTAGACCCCATCCTGAA
GCTATCTACAGGCCCTGCCATGAGTTAGCTCATTAAACATAACAAAGACAC
TTATATTACTCAGAAAATTCCAACAGTTTTTAGAAGCTCCATGTCAGGAAC
CTGGGACATAGATCAAATTCTTTTTTTTTTTTTTTTTTTGGAGACAGGGT
CTTGCTGTGTTGCCAGGCTAGAGTGCAACGACAGATCACAGCTCAATGC
AGCTTCAACTTCCCAGGCTTAAGTGACCTTTCACCTTAACCTTCCAAGT
ATCTGGGACCACAGAAAATGGCTAATTATCCTGGCTGATTTTTTAACTTT
TTTTTTTTGTAGGGATGGGATCGCCCTGTGTTGCCAAGGTTGGTCTCAA
CTCCTGGGTTCAAGCAATCATTCTGCCCTGGCCTCTGTGATGGTTAATAC
TGAGTGTCAACTTGATTGGATTGAAGGATACAAAGTATTATTTTTGGGTG
TGTCTGTGAGGGTGTGCCAAAGGAGATTACATTTGAGTCAGTGGACTGG
GAAAGTCCACCCTTCCCAGTGGACTGGGAGACCCACCCTCAATCCAGGT
AAACACAATCTAATCAGCTGCCAGTGTGGTCAGAATAAAAGGAGGCAGAA
GAACAGGGAAACACTAGACTGGCTTAGTCTTCCAGCCTACATCTTTCTCT
CATGCTGAATGCTTCCTACCCTCGAACATCAGCCTCCAAGTTCTTCAGTT
TTTGGACTCTTGGACCTTCAACCACAGATTGAAGACTGCAGTGTGGCTT
CCCTGTTTTTGGAGTTTTTGGGACTCAGACTGGCTTCCTTGCTCCTCAGCT
TGCAGATGGCCAATTGTGGGACTTTAACTTGTGATCATGTGAGTCAATAT
TCCTTAATAAACTCAGATATATATATATGTATCAGACATATATATATATC
CTATTGTATATTATATACAGATATATAATATCCTATTATATACAGATATA

FIG. 3 (24 of 52)

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TAATATCCTATTATATACAGGTATATATATATATATGTATCATATATAIA
TATCCTATTGGTTCTATCCCTCTTGAGAATCCTGACTAATACAGCCTCCC
AAAATGCTGAGATTACAGGAGTGAGCCACAGCCACCATGCCCAGCCCCAA
ATTCTTAATTATACAACAATGGGTCCAGAGATCAGGGCCTGGGTAGGATG
CAGCAATAAGAAAACAGATGGTGGATGGGGACACATGTTGGAAGTGTGGC
AGGACATGGCTGAGGGAACATAGGATGGTGTCTATTTTCATGGCTGAG
TGTGAGGAACAGCATAAGGTCAAAATTTAGGTCAATGGTGAGTTTTTTA
AATTGTTGCTGTGAACCCCAAAAATCTGACCCAGGTCTCAGTTAATTTAG
AAAGTCTATTTTTTCCAAGGTTGAGAACACCCACCCACTCACGACAAGAGC
ATCAGGAGGTCTGACCACATGTGCCCAAGGTGGTAAGAGCACAGCTTGG
TTTTATATATTTTAGGGAGACGTAAGTCATCAATCAATATATGTAAGATG
TACACTGGTTCTGCCTAGAAAGGCAGGACAACTTGAAGCAGGGAGGGGGC
TTCCATGTACAGGTAGGTGAGAGACAAACAGTTGCATTCTTTGAGTTTC
TGATTATCCTTTTCAAAGGAGGCAATCAGATGTGCAATTATCTCAGTGAG
CAGAGGGATGACTTTGAATAGAAAGACAGGCAGGTTTGCCCTAAGAAGTT
CCCAGCTTGACTTTTTCTTTAGCTTTGTGATTTGGAGGCGCCAAGATT
ATTTTCTTTTACATTTCCCCCTTTCTTTTAAAGAATCTTTTAAAGAA
AGCTTTTAAAAAGAAAATGAGTCTCTGGTCCCAGGTTTCATCTGAATTCT
CGAGGGGAGGATGGTTTATCCTAACGGGTGGTTCTGAATTTTGAGAAAG
TGCATTGTAC

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AAAAGCCATACGAATGAGGAAGAATTAAGGGCCAGAACAAAACAAGAAGA
TGAGGGAAAGTTTGGAACCTTCTTAGAGACTGGCTAAATGGTTGTGACCAA
AATGCTGATAGTGATACGGACAATGAAGTCCAGGGTGACAAAGTCTCAGA
TGGAAATGGGGAATTTGTTGGGAACTGGGCAAAGGTACCCCTTGCTATGA
CTCAGCAAAGAAATTGGGTGCATTGTGTTTCATGTCCTGGGGATCTGTGGA
AGTTTGAATGTAAGAGTGATGACTTACGGTAGGGTATCTAGTGGAAGAAA
CCTCTAAGCAACAAAGTGTGTTGCTTAGAAATTTCTTTCTTTCTTTTTT
TTTTTTTTTTGAGCTGGAGTTTTGCTGTGTGCGCCAGGCTGGAGCGCAGTG
GCGCAATCTTGGCTCACTTCAAGCTCTGTCTCCTGGGTTCATGCCATTCT
CCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGCGCCTGCCACCATAC
CTGGCTAATTTTTTTAGTATTTTAGTAGAGACGAGGTTTCACCATGTTAGC
CAAGATGGTCTCAATCTTCTGACCTCGTGATCCACCCGCCTTGCCCTCCC
AAAATGCTGGGGTTACAAGCATGAGCCACCCCGCCTGGCCTGCTTAGAAA
TTTCTAAGCCAGGATATGGCCTGTCTGCTTCTAACAGCCTGTGCTCAGGG
GTAAGAAATGACTTAAAGTTGGAACCTATGTTTAAATGGAAGTAGAGT
CTAAAAATTTGGAATTTGTCAGCCTGGCCTTGTGGCAGAGAAAGAATCC
AAGTAGGCTGCAGAGCAATCATTGCTAGAGAGATTAGCATGACTAAAAGG
GAGCCAAGTGCTAATATTCAAGACAATGTTAAAAAGGCCTTGAGGGCATT
TCAGAGATCTATGAAGCAGCCCTCCCATCACAGGTGCAGAGGTTTGGTG
CACTAGGCCCAGAGGTTTTATGGGCCANNGCCAGGGCCACACTGCTATGC
ACAGCTTTGGGACACTGCTGCCCGCATCCAGGCCACTCTGCTCTGGCTCC
ACCCCTTGGCTCAAACGGGGCCAAGATAGAGCTTGGACCACTGCTCCCGAGG
GCACAAGCCATAAGCCTTGGTGGTTTCCATGTGGTGTAAAGCCTGCAGGT
GCCCAGAATGCAAGATTGAGGGAGCTTGGGCACTTCCACCTAAATTTTCA
AGGATGTGTGAGAAACCTAGGTTCCAGGCAGAAAGCATGATACAGGGGC
AGAGCCCTTGCAGAGAACCTCTACTAGGGCAATGCCAAAGGAAAATGTGG
GGTTGGAGTCCTCACACATGGTCCCCACTGGGGCACTACCTGGTGATACT
GTGGGAATGGGGCTGCTGCCCTCCAGACCCCAAGATGGTAGATGCACTGG
CAGCTGGCACCCCTGAGCCTGGAAGCTGCAGGCACTCAACTCCAACCCA
TGAGATCAGCCACATGGGCTACTCCAGGGAAGCCACAGAGGCAGGGCT
GTCTAAGGCCTTGGGAGCCTACCCCTTGAACCAGCTTGCAGGACATGGAA
TCAAAGATTATGTTGCAGCTTTAAGGCTTAATGTTTTTCCCTGTCAATTT
AGGCTTGTGTGGGACCTGTTGCTTTTTTTTTTTTTTTTTTTTTTTTGGT
CACAGGTGTTTGAACCAGAAATTCATCTTGAATAGGGGCTGGGTAAA
ATAAGGCTGAGACCTACTGAGCTGCATTCTAGGAGGTTAGGAATTCTAA
GTCACAGGAGGAGATAGGAGGTCCGCACAAGATACAGGTAGCGAAGACCT
CGCTGATAAAATAAGTTGCAGTAAAGAAGCCAGCCAAACTCACAAAGCC
AAAATGGTGATATGGTTTGGCTCTATGTCCCCACCCAAATCTCATCTCAA
ATTATAATTCCCATAAATCCCCACATGTTGAGGGGAGGACCTGGTTGGAGG

TGATTGGATTATGGAGGCAATTTCCCCCATGCTGTTCTGGTGATACTGAG
TGAGTTCTCATAAGATCTAATGGTTTTATAAGTGTGGAAAGTTCCTCCT
ACACACATGCTCACACTCTCTCCTGCAGCTTTATGAAGAAGGTACTTGCT
TTCCTTTCTGCCATGATTGTAAGTTTCTTGAGGCTTCCCAGCTATGCAGA
ACTGTGAGTCAATTAAACCCGTTTTCTTTATACATTACCAGTCTTGGGCA
GTTCTTTACAGCAGTGTGAGAACTGCTGGCGATGAGAGTGACCTCTGGTT
GTCTCACTGCTCATTATATGCTAATTATAATGTATTAGCATGCCAAAAG
ACACTCCCACCATGACCCCAACAGTCATGCCTGTGCCGGTCTCAGCACCA
TGACAGTTTACAGATGGCATAGCAACGTCTAAAAGGTACCCCATATGGAC
TAACAAGGGGAGGAACCCCTCAGCTCTGGGAAGTGCCTACCTCGTTCCCAG
AAAGCTTGTGAATAATCCACTGCTTGTTTAACATATAATTAAGAAATAAC
TATTAAGCATCCTTAGTTTCAGCAGCCCAAGCTGCTGTTCTGCCTATGGAG
TAGCCATTCTTTATTCCGTTACTTTCTTAATAAAATTGCTTTTACTTTAC
TGTATGTACTCGCCTGGAATTCTTTCTTGTACGAGGTCCAGAGCCCTCTC
TTGGGTCTGGATCGGGACCCCTTTCTGGTAACATTTTGACCAATTTCTCC
CTTCTGGAATGGGAATGTTTACACAATGACTGTATCACTTTTGAATCTTG
GAAGTAAATAATTTGTTTTTGACTTTACAGCCTCATAGGTGGAAGGAACT
TGACTTGAATTTTCAGATGAGACTTTGGACTTTGGGACTTTTGGGTGGGG
CTGGAATGAGTTAAAAGTTGGGGGGATTATTGGGAAGGCACGATTTTATT
TTGCAATATGAGAAGCACATGAGATTGGGGGACCAAGGGTGAATAATA
TGGTTTGGATGTTTGCCCCCTCCAAATCTCACATTGAAATGTAATCCCCA
GTGTTGAAGTGAGGCCTGCTGGAAAATGTTTGGATTACAAGGCTGTGAG
CACATTGGATAAGACGTGTAGGNCCC

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CGCAGCTCGCTGGTTAATTCTGTGGCTCCTGTGACCACTATTATAGCACC
AGGTCTATGACCAGGAGAATTAGACTGGCATTAAATCAGAATAAGAGATT
TTGCACCTGCAATAGACCTTATGACACCTAACCAACCCCATTTTACAA
TTAAACAGGAACAGAGGGAATACTTTATCCAACCTCACACAAGCTGCTTTC
CTCCCAGATCCATGCTTTTTTTGCGTTTATTATTTTTTAGAGATGGGGGCT
TCACTATGTTGCCACACTGGACTAAAACCTCTGGGCCTCAAGTGATTGTC
CTGCCTCAGCCTCCTGAATAGCTGGGACTACAGGGGCATGCCATCACACC
TAGTTCATTTCTCTATTTAAATATAACATGGCTTAAACTCCAACCTGGGA
ACCCAAAACATTCATTTGCTAAGAGTCTGGTGTCTACCACCTGAACCTAG
GCTGGCCACAGGAATTATAAAAGCTGAGAAATCTTTAATAATAGTAACC
AGGCAACACCATTGAAGGCTCATATGTAAAATCCATGCCTTCCTTTCTC
CCAATCTCCATTCCCAAACCTTAGCCACTGGCTTCTGGCTGAGGCCTTACG
CATACCTCCCGGGGCTTGACACACACCTTCTTCTACAGAAGACACACCTTG
GGCATATCCTACAGAAGACCAGGCTTCTCTCTGGTCCTTGGTAGAGGGCT
ACTTTACTGTAACAGGGGCCAGGGTGGAGAATTCTCTCCTGAAGCTCCATC
CCCTCTATAGGAAATGTGTTGACAATATTCAGAAGAGTAGGAGGATCAAG
ACTTCTTTGTGCTCAAATACCACTGTTCTCTTCTTCTACCCTGCCCTAACC
AGGAGCTTGTACCCCAAACCTCTGAGGTGATTTATGCCTTAATCAAGCAA
ACTTCCCTCTTCAGAAAAGATGGCTCATTTTCCCTCAAAAGTTGCCAGGA
GCTGCCAAGTATTCTGCCAATTCACCCTGGAGCACAATCAACAAATTCAG
CCAGAACACAACCTACAGCTACTATTAGAACTATTATTATTAATAAATTCC
TCTCCAAATCTAGCCCCCTTGACTTCGGATTTACGATTTCTCCCTTCCTC
CTAGAACTTGATAAGTTTCCCGCGCTTCCCTTTTTCTAAGACTACATGT
TTGTCATCTTATAAAGCAAAGGGGTGAATAAATGAACCAAATCAATAACT
TCTGGAATATCTGCAAACAATAATATCAGCTATGCCATCTTTCCTACTA
TTTTAGCCAGTATCGAGTTGAATGAACATAGAAAATACAAACTGAATT
CTTCCCTGTAAATCCCCGTTTTTGACGACGCACTTGTAGCCACGTAGCCA
CGCCTACTTAAGACAATTACAAAAGGCGAAGAAGACTGACTCAGGCTTAA
GCTGCCAGCCAGAGAGGGAGTCATTTCAATTGGCGTTTGAGTCAGCAAAGG
TATTGTCCTCACATCTCTGGCTATTAAAGTATTTTCTGTTGTTGTTTTTC
TCTTTGGCTGTTTTCTCTCACATTGCCTTCTCTAAAGCTACAGCCTCTCC
TTTCTTTTCTTGTCCCTCCCTGGTTTGGTATGTGACCTAGAATTACAGTC
AGATTTTCAGAAAATGATTCTCTCATTTTGCTGATAAGGACTGATTCGTTT
TACTGAGGGACGGCAGAACTAGTTTCCTATGAGGGCATGGGTGAATACAA
CTGAGGCTTCTCATGGGAGGGAATCTCTACTATCCAAAATTATTAGGAGA
AAATTGAAAATTTCCAACCTCTGTCTCTCTTACCTCTGTGTAAGGCAAA

FIG. 3 (26 f 52)

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TACCTTATTCTTGTGGTG'TTTTTGTAACCTCTTCAAACCTTTCATTGATTG
AATGCCTGTTCTGGCAATACATTAGGTTGGGCACATAAGGAATACCAACA
TAAATAAAACATTCTAAAAGAAGTTTACGATCTAATAAAGGAGACAGGTA
CATAGCAAACCTAATTCAAAGGAGCTAGAAGATGGAGAAAATGCTGAATGT
GGACTAAGTCATTCAACAAAGTTTTTCAGGAAGCACAAAGAGGAGGGGCTC
CCCTCACAGATATCTGGATTAGAGGCTGGCTGAGCTGATGGTGGCTGGTG
TCTCTGTTGCAAAAGTCAAGATGGCCAAAGTTCCAGACATGTTTGAAGA
CCTGAAGAACTGTTACAGGTAAGGAATAAGATTTATCTCTTGTGATTTAA
TGAGGGTTTTCAAGGCTCACCAAAATCCAGCTAGGCATAACAGTGGCCAGC
ATGGGGGCGAGGCCGGCAGAGGTTGTAAAGATGTGTACTAGTCCTGAAGTC
AGAGCAGGTTTCAGAGAAGACCCAGAAAACTAAGCATTTCAGCATGTTAAA
CTGAGATTACATTGGCAGGGAGACCGCCATTTTAGAAAAATTATTTTGA
GGTCTGCTGAGCCCTACATGAATATCAGCATCAACTTAGACACAGCCTCT
GTTGAGATCACATGCCCTGATATAAGAATGGGTTTTACTGGTCCATTCTC
AGGAAAACCTTGATCTCATTTCAGGAACAGGAAATGGCTCCACAGCAAGCTG
GGCATGTGAACCTACATATGCAGGCAAATCTCACTCAGATGTAGAAGAAA
GGTAAATGAACACAAAGATAAAATTACGGAACATATTAACTAACATGAT
GTTTCCATTATCTGTAGTAAATACTAACACAACTAGGCTGTCAAATTT
TGCCTGGATATTTTACTAAGTATAAATTATGAATCTGTTTTAGTGAATA
CATGAAAGTAATGTGTAACATATAATCTATTTGGTTAAAATAAAAAGGAA
GTGCTTCAAACCTTTCTTTCTCTAAAGGAGCTTAACATTCTTCCCTGA
ACTTCAATTAAAGCTCTTCAATTTGTTAGCCAAGTCCAATTTTACAGAT
AAAGCACAGGTAAAGCTCAAAGCCTGTCTTGATGACTACTAATTCAGAT
TAGTAAGATATGAATTACTCTACCTATGTGTATGTGTAGAAGTCCTTAAA
TTTCAAAGATGACAGTAATGGCCATGTGTATGTGTGTGACCCACAACAT
CATGGTCATTAAAGTACATTGGCCAGAGACCACACTGAAATAACAACAAT
TACATTCTCATCATCTTATTTTGACAGTGAAAATGAAGAAGACAGTTCCT
CCATTGATCATCTGTCTCTGAATCAGGTAAGCAAATGACTGTAATTCTCA
TGGGACTGCTATTCTTACACAGTGGTTTCTTCATCCAAAGAGAACAGCAA
TGACTTGAATCTTAAATACTTTTGTTTTACCCTCACTAGAGGTCCAGAGA
CCTGTCTTTCATTATAAGTGAGACCAGCTGCCTCTCTAACTAATAGTTG
ATGTGCATTGGCTTCTCCCAGAACAGAGCAGAACTATCCCAAATCCCTGA
GAACTGGAGTCTCCTGGGGCAGGCTTCATCAGGATGTTAGTTATGCCATC
CTGAGAAAGGCCCCGAGGCCGCTTCACCAGGTGTCTGTCTCCTAATGTG
ATGTGTTGTGGTTGTCTTCTCTGACACCAGCATCAGAGGTTAGAGAAAGT
CTCCAAACATGAAGCTGAGAGAGAGGAAGCAAGCCAGTTGAAAGTGAGAA
GTCTACAGCCACTCATCAATCTGTGTTATTGTGTTTGGAGACCACAAATA
GACACTATAAGTACTGCCTAGTATGTCTTCAGTACTGGCTTTAAAAGCTG
TCCCCAAAGGAGTATTTCTAAATATTTTGAGCATTGTTAAGCAGATTTT
TAACCTCCTGAGAGGGAACCTAATTGGAAAGCTACCACTCACTACAATCAT
TGTTAACCTATTTAGTTACAACATCTCATTTTTGAGCATGCAAATAAATG
AAAAATCTTCCTAAAAAAATCATCTTTTTATCCTGGAAGGAGGAAGGAAG
GTGAGACAAAAGGGAGAGAGGGAGGGAAGCCTAATGAAACACCAGTTACC
TAAGACCAGAATGGAGATCTTCCTCACTACCTCTGTTGAATACAGCACCT
ACTGAAAGAACTTTCATTCCCTGACCATGAACAGCCTCTCAGCTTCTGTT
TTCCTTCCTCACAGAAATCCTTCTATCATGTAAGNTATGGCCCACTCCAT
GAAGGCTGCATGGATCAATCTGTGTCTCTGAGTATCTCTGAAACCTCTAA
AACATCCAAGCTTACCTTCAAGGAGAGCATGGTGGTAGTAGCAACCAACG
GGAAGGTTCTGAAGAAGAGACGGTTGAGTTTAAGCCAATCCATCACTGAT
GATGACCTGGAGGCCATCGCCAATGACTCAGAGGAAGGTAAGGGGTCAAG
CACAATAATATCTTTCTTTTACAGTTTTAAGCAAGTAGGGACAGTAGAAT
TTAGGGGAAAATTAAACGTGGAGTCAGAATAACAAGAAGACAACCAAGCA
TTAGTCTGGTAACTATACAGAGGAAAATTAATTTTTATCCTTCTCCAGGA
GGGAGAAATGAGCAGTGGCCTGAATCGAGAATACTTGCTCACAGCCATTA
TTTCTTAGCCATATTGTAAAGGTCGTGTGACTTTTAGCCTTTCAGGAGAA
AGCAGTAATAAGACCACTTACGAGCTATGTTCCCTCTCATACTAATATGC
CTCCTTGGTCATGTTACATAATCTTTTCGTGATTTCAGTTTCTCTACTGT
AAAATGGAGATAATCAGAATCCCCCACTCATTGGATTGTTGTAAAGATTA
AGAGTCTCAGGCTTTACAGACTGAGCTAGCTGGGCCCTCCTGACTGTTAT
AAAGATTAAATGAGTCAACATCCCCTAACTTCTGGACTAGAATAATGTCT

FIG. 3 (27 of 52)

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GGTACAAAGTAAGCACC_AATAAATGTTAGCTATTACTATCATTATTAA
ATTATTTTATTTTTTTTTTTTTTTGAGATGGAGTCTCACTCTGTTGCCAGGC
TGGAGTGCAGTGGCGCAATCTTGGCTCACTGCAAGCTCTGCCTCCTGGGT
TCACGCCATTTTCCTGCCTCAGCCTCCCGAGTAGCTGGGACAACAGGCAT
GTGCCACCATGCCAGCTAATTTTTTTTGTATTTTTTAGTAGAGATGGGGTT
TCACTGTGTTAGCCAGGATGGTCTCTATTTTCTGATCTCATGATCCGCCT
GCCTTGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACCGCGCCCCG
GCTTATTATTATTATTACTACTACTACTACCTATATGAATACTACCA
GCAATACTAATTTATTAATGACTGGATTATGTCTAAACCTCACAAGAATC
CTACCTTCTCATTTTACATAAAAGGAACTAAGCTCATTGAGATAGGTAA
ACTGCCCAATGGCATAACATCTGTAAGTGGGAGAGCCTCAAATCTAATTCA
GTTCTACCTGAGTAAAAAATCATGGTTTCTCCTCCATCCCTTTACTGTA
CAAGCCTCCACATGAACTATAAACCCCAATATTCCTGTTTTTAAGATAATA
CCTAAGCAATAACGCATGTTACCTAGAAGGTTTTTAAATGTAACACAAT
ATAAGAAAATAAAAATCACTCATATCGTCAGTGAGAGTTTACTACTGCCA
GCACTATGGTATGTTTCTTAAATCTTTGCTATACACATACCTACATGT
GAACAAATATGTCTAACATCAAGACCACACTATTTACAACCTTTATATCCA
GCTTTTCTGACTTAGCAATGTATTGATGACATTATGCATGCTTAGACCTC
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GTATTCTATTCTCGGTTATAACACAATCACAGTGATTTGTCATATCTTTC
CAGGATTTGTTAATTTCACTTCTTCAGCTGTTTCCCCCTTGTTGGCTGGA
ACTGATTTTCTATCTTCTGGGAGAATCTTCAGCAAGCCAACTCAGGATTT
GTTGGGTGCATTTTGTCAAGTCTAGGACCCAGGCTCTGGGTGACTGATTT
CCTCTAATTACCGAGCAATGTAAATGAGGAAGTCTGATTGTGTAAAGGT
GTTAAACTTTTGTGTGACGGCAAACTTTAATACCATGAATAGAGATTCC
AGAATTTTCCAACCTTCTAACGGGATTCTTCTCACTCCCTGACATTAGAAT
GTTAGAAAATCTACCACAAAACATCTGTGAGGCTATCCTACAAGGCCCGT
TTTTCAAAATAGGTTTTTACAAGGATTGCTATTTGGGATGATAGTTTCAG
AAAGGCGCTATCAAAGTTAATTGATGATGTGTGCAAGCTGAAAGTTATAT
GTTAGAAGTAGCAGTGATTTCAAAAATATCCCTTTTAGGCTTTTGTCTAA
TATATCTGCTCATTTTCAAAGTTCCCAATATTATAAACTTTTTTAAAGCA
GAAAGAAGAACCCTCCATTTCTGCTGGCCCCCTTCCCTGTTCAACTAAAAA
GTATTTTCCCAGGCAATGCTATCCCAGGACTCACACTCCATCCATCCATC
ACCTACCATAAGTTCTTTGAAGGGCTCATTCTGAGCGCTTCCCTGAGTGCC
TGGGATCTGTTATTTCTCTCCATTTCTGCTGCTGCATGGTAGTCCAAGTC
CTCCTCCCTTTTCCCCTAGGCCATTTGAATCATCTGCTAATTGGTTTTCC
TGATTGCCACGGAACTTCTCCATCCCTTCTCACATATCAGCCACAGA
AGTATCTCCAAAAGCAAATCTGGTGACATGAAGCCCTTGACAAAACCC
ATTCATTACTGGTTCCACACCTCCTTTGTGGATAAGTTCAAGCTCCTGAG
TGTGGCAAGCAGGGCCCACCTGGAATCCCCTGCCCTCCTCTCCTATCCCA
CGCATCAATCTTTCCTGTCTATTTGCAGTTCCTTGAATGTGATATTCTTT
CTAGTCTCTGTGCTTTTGCATAACCTGTTCTTCCCTGACTGGAACTCCTT
CTCCTCCTTGTAGTTTGGCTAATTTCTAGTCTTTCAAGACTCAGCTCATG
CTTCACCCCTCTATAACAAGTCCTTTCCCAAGCTGGGTGGTGGATGCTC
CTCTGTGCTGTGTGAGTCTTGAACATCCTCAGCAAACCTCAGCTTTGTTT
GCTTGTCTCCCTTGCTGTCAATGCACCTGATTCAGGGCTGGCATATACTG
TTCACCTCCATGACTGGCTCATGGTGGTGCTCCGTGAATATCATCCACCC
AAACGGATGAGAGCTACCATGCCATCACTTGTGACTTCCATCTGGAGCTA
ACCTCCCCCGACAGGAAAGCGTTTCCTTAGGAAAGAAATATCTTTGGGTTA
AATAGAAGTAGAGACTCACCAGAAGCACTATGTCCAGCTCAGAATGAACT
GCTCAGTAAGCAGCCTTGTCAATGAGGAGGCAGCAGGCCAGCCCCAGAGG
CCTCAAAGTGGGAGAGTAGAGAAGCGCAGTTCCTGCCACAAAGGCACAGT
GGACACCTTGCTCCCCTGGCTGGCTGGAAGCAGATGGTGTCCACCTGCTT
CCATGGGAATTCTGCACCTTTAATAAAGTTTTATGGGACAGGAAGGTGAC
TGGCATTGACATTGTAACGAGGAATGGGTGGTGCCACCTTTGCTGTGTCT
TACCAGAAATACCTGTGGCAGGTAAATTTCTAGAGAGACCTCCCATTTTC
TCCCATATAGCAATTTTGAAATGTTTCTGAGGGCTTTCCAAATTCATCT
GGGAACATAGGAGTTCCAGAAAGATGAAATCAAAGGTGATGGTATGCCAA
AGAAAGTAGCTTTTAGAATGACTTACATTAGCCATTATCCATTACAGCAC

FIG. 3 (28 of 52)

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FIG. 3 (29 of 52)

AGTATGGGAGTTCAGAGGATAGGGGGTAAATGAGGGGAGTAGGTGGGTAGA
AAAGGTTAAAAGTAAATAATGATGGGAAGGAAGACAAAAAGACGACAGGG
GTGCCAAAGGACTCTTAACCTCATCTGAACGGAGTTGCCCTGTTTTGCTC
TCTGATGCTCATGTATCTATCCTTAGAGACAGCTTGGCGGGCAATGTAGA
GCGTAGGGGCTGACATAGGGGGTGGAGTCCCACCTCCGTGACTTCTAGC
AAATTAGCAAACCTTTGCTGCTGCTAAGCCTATAAGGCGGACAGAAATGCC
ATCTTTAAAGCTTGTTATGTAAAGTGCCTAGGACCTCGTAGGCATCAACA
GGAATAATGGATGAAACAAAACAACGGTGCCTATCTTGAGAGAAAGTGGCA
TCTGAGCAGGAGTATTTTGAAAGGTAGGAAAGGGCTCCAAGCACATCTAA
GAGATTAGGGAACGCAGAGCCTTAGCCCTGGGTGCAGATTTAACCAATC
AACTTCTAACCACCGCAGGCTGAGAGGTGTGGAGTGAGAGCCCCGCCAGA
GGCAGGAGACCCGGGCTTCGGCCAGACCCCGCCTCCTGGTACAGAGGACC
ACGCCCCGCTCTGCCTGGAGCCAAATGTGGATCAAAACAGCGCGCAGCTT
CCCCTGCTGGTGAAAACCCGAGCAAGGGGCTCAGTTTCTTTATCCGGA
ACGTGGTGACAATGACATCTCTTTGCAAGGCTGCTGCAGGGCTTTCTGGA
AATACGCCCCGTGAGGTATCTGGGCCTGCGCACAGCCTCCCCCGCCCAGGA
CCCAGACGTCTACCTGGGGGTCCCGTCTGCGCTCCCGGGATGGAAAACGC
CCAGGGGAAACTTAGGCAGGCGAGCGGACGGGCACCTCCCGCGGGACGAA
CTCACTCGGTGGCCTCCTACTTCCCCGGCCGTGTTCCAACGCCTGAGAAT
AACGGGAACAGCGGTCTACTCACCGACAGCGGCAGCAGCGGTAGGCCCCG
GGCCCCACCATGACTCTTCAGTGACAGTTTTTCTTCAAACGCCGCSCTG
TAGCCAGGACCGGCGTGCCGCGCGTCCACGCGTCTCATTGGCTCCTGCG
GGTTTGAAACTCGCTAGTCGTACGACGGGAGGGCGGGACAACAGGCAAT
AGGCTCTTTGCGGTGGCTCTGGCCTTGAGAACCCGACCTTGGGGCCCTT
TGATTGGAAGAAGCTGCAGCGCACCTCGGCATTGAGGGCGGCTTCTCGG
GGCGCGGCGCCCGCCCGCTCTGAGTGCGCCTGTGAGTGCGCCTCCGAGTG
GGCGTGGGACCCCTCCGTGGGGGCCTCAGCCGGGCTGGTGGTTGGGGGGCG
GTTACGCTGAATCCAGCTGGGGTTGGCGCGCCGGGAGTCCCTGGGCGGAG
AGACAGGGCGGTCTCCAGGATGCTGGGGCCGCTACCTGATTCTGTCCT
TTCAAAGTCTCAGACTCACAGGAGCTGTGAAAAATAATATTATAAAGAG
GACATATGGGTCTTATGCATCTAAAGGCTCCTAGTTCTTAGTACTGCAGG
GTGGCTCGTTTAATTGTGGTAAAATATGCATAACATCACATATAACATTT
TAACCATTTTAAAGTGTTAAATTTTTCAAATGTGCAGTTTAGTGGTAT
TAAGTACCCTCACATTGTGGCACAGCCACCCTACTGTCCTTTCCAGAAC
TTTTTCATCTTCCCAAATGAAACCCGTGACCCGCTCACTAACTCCGCACTC
CTCCCTCCCCCAGCCCCAGGCAATCACCATTCTAGTTTCTGTCTCTATGG
ATTTGACAACTGTAGGTGCCATATAAGTAGAATCATGCAGTATTTGTTCT
GTGACTGGCTTGTTTCACTTAGCATAAAGTATTCAAGGTTTATCCATGTG
TAGCATGTGTCAGAAATTTCTTTCTTTTAAAGGGGAATAGCATTTCGTT
GTGTGGAGATGCCACATTTTGCTTCTTGGTCCATCCCTCTCCGGACACTT
GAGTTGCTTCCACTTTTTTGCTATTGTGAATAATAATGAACATGAATG
CACAAATAACTCTTTGAGACTCTCCTTTTCACTTTTGGGTATATACCA
CGAAGTGGTATTGTTGGATCAAACGGCAATTCTATTTTTTAATTTTTTGAG
AAACTGCCTTACTCCTCTCACGGTGATCTCTTGTTCAAGGTATATTTTCG
ATTTACCTGATCAGCTGACTATAAGGCCATAAGGCTAACGGAGAAACGC
AGGCCTAGTTTCTCCTAGTTACTAGGAGATCGCAGGCCTCGTTGTCCTGA
ATCCCTAGACACACTTCATTCCCCTTGTTTTAATCCTAAATTTTTTTTCT
TTTGAAGTTTGTCTGTTTCACTATTCTCCAGTTTCTTAAAGAGGTCTG
GAAAATGCTTTTGGCTCCTTGTTGTATGAAGGTTCTCTTCCATGGATGCT
GGAGAAGTCGTGTGTGGAGGGGCAGTCATATCTGGGCACCTGTTGGCCAG
GTTACGCTTACCAGTTGGGTACTCAGCAGGGCATGAAGCCACTGCAGCAG
CCCTTCTCTTAGCCGTAAATAGGGAGTTTGGGAAGAGAGCCAGGGTTTCT
GGATTTATGCATTTTGATATTTTCAATAGTGTATTAAATGTTTAAATAG
GAAAACCTGATCATTATTTTGTAAATGACTGAGAAAGGGACTCCTTCACC
AACAGTTTCAGAAAAGTGAAGGCGGTTTTGTTTTGGTCTTTGTAGAATCT
AGGTGGTTGAATGCATGTGAGTTGTAGAAGTCACCTTGCCTGATATCCCA
CGCAGTGCTGGAGTATTCACAGACCCCATGTAGGTACTGCACCTTTGCA
GGTATACTGCTGGTGTGGTGAGCTGCCTTACCTGTCTGTTATTGGAGA
CCCCCTGCTTATTAGGAACTTAAATGAACTCAAATGAGCTTCTTGCTT
ACTGGTCTAGTCCTTTGGAGCAACATAGGCCAGTTCTGCCTCGTTTTTT

FIG. 3 (30 of 52)

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TCCATCCTTTGGGTATTTGACGGTCTATTTTGTAGGACACAAAATGTGGG
 AAAATAGCTAGGCAGGTTTAAAAATTCTCAACTCTACCAAGCATGGTGGC
 TTATGTCTGTAATCAATCCCAGCACTTTGTGAAGCTGAGGCAAGAGGATT
 GCTTGAGCCTAGGAGTTTGAGACCAGACTGGGCAACATAGCAAGACCTCG
 TTTCTTAAAAAATAAATAATTACAAAATTAACCAGGCATGGTGGCA
 CACACCTGTAGTCCCTTCTACTCAGGAGGCTGAGGTGGGAGGATCACTTG
 AGCCCAAAAGTTGAAGGATGCAGTGCAGTGTGGTCATGCCACCGCACTCC
 AGCATGGGAGGCAGAGCAAGACCCTGTCTCCAAATAAATACATAAATTAA
 ATTCTTAACTCATTCATCAAAGTATCCACTGTAGCTTTCCATCATCCTGG
 TGTGTTTTTTTTTAGAAGGATCTGGCTCCATTGCCCGGCTAGAGTGCAGT
 GGCATGATCTCAGCTCACTGCAGCCCCACCTCTCTGGCTTAAGCGATCA
 CCCACTTCAGTCACCCATCTGGGTAATTTTTGTATTTTTTGTAGAGATGG
 GGTTTTGCCATGTTGCCCCAGGTTGGTCTTGAACCTCTGGCTCAAGCGAT
 CCATCTGCCTCCATCTCCTAAAGTGTGGGATTACAGGTGTGAGCCACCA
 CACCAGGACAATCCTGGTGGCTTTTAACGGTTTTCCATTGCTCTCAGGCT
 AATGACCTATAAGCCCCCTGCGGGCTTGGCCTTTTACTCCCTEAGCATTAG
 CCACCTCCCTTAGCCTTAGCCCACACTACTCTCCCCTTGCTCAGTGTTAT
 CCAGACACTTTGTTTTTTTCTTTCCATACTCCTCTCTGTCTGGGAATCCA
 ACCTTTCTTTCTCATTTCTCTAGTTGATTATTATTATTTTTTACTCTAGCA
 GCCTTATTGAGATATTTACATAACCGTACGATTCTCCCACTTACAGTGTAC
 AATTCAATTTTCTAACATTTTCATCACCCCTAAAGAAACCCTATACTCA
 TTAGCAGTCACTCCCCATTCTCCCCTCCTCTCAGCCCCCTAGAAACCATGA
 ATCTACTATCCATCTCTATAGATTTGCCTTCTGGACATTTTCATATGTATG
 AAATTATGCAATTTGTGGTCTCTGATGGGCTTCTTTTGTACCAAATAT
 CATGGGTTTGATCTAGGTCTGCTGCTCGCTGCACAGAAAGCCAGCCACT
 GAGATGACAAGTATTGCCAAGGAAGAAGGCTTTAGTCAGGTGCTGCAGCT
 GAGGAGATGGGGGCTCAATCTCAAATCCATCTCGCTGACCTAAAACCAGG
 GGTTTGGATAGCAGGGAAGAAATGTAACAATGCGTAAGAAAACAGGAACC
 AGGGAGGGGCAAGGAAGCAATCCTGATGAATGAGTGGTCCAAAGTCTCAT
 TGCCTGGATGTGGTGATCTGGCGAGTTTCAGTTCTTTGATACTTTTTTTG
 AGAGGCCTGAAGTCTTTTCCCCAGGAAGGAAGTCAAACAAAACAAATACA
 AGCTTCCAGCTTTAAGACCAGAAGCGTCAATTTCTATGTTTATCCGAAAG
 AACAGTCTATGGGACTATTGGTTAAGTTTCACTTTCACTTAGTATGCTGT
 TTTCAAGGTTTATCCACATAGCATGTGTCAGTACTTCATTCTTTTATGAC
 TGGGTATTCTATTGTGCGGATATACAATATTTTATTTGCCATTCATCAGT
 TGATGGACATCTAGGTTCTTTCCACTTTTTGGCTATTATGAATAATGCTG
 TTATGAACTTTTCATGTATAAGTTTTTGTGTAGACATATGTTTTCAACACT
 CATGGGTATATACCTAATGAGAGGAATTACTGTGTCATACGATAATTCTA
 TCTTTAACCATTGAGGAAGTCCAGACTGTTTTTCAAAGCAGCTGCAGC
 ATTTTACATTCTACCAGCAGTGTATGAAAGTTCCAGTTTCTTTACATCC
 TCAACAACACTTGTTATTGTCCATCTTTTAAATTACAACCATCCTAGTGG
 TTGTGAAATGGTATCACATTGTGGTTTTTATTTGTATTTCTTGATGACT
 AATGATGTTAAGCATCTTTTTATGTGTTTACTGGCCATTTGTATATCTCT
 ATTCAGAGTCTTTGCCAATTTTTAAATTGGGTCAGTTGTCTTCTTCTTTT
 TTTTTTGAGATGGAGCCTCACTCTGTTTCCCAGCTGGAATACAGTGGTGT
 GATCTCAGCTCACTGCAACTTCCACCTCCTGTGTTCAAGTGATTCTGGTG
 CCTCAGCCTCCCAAGTAGCTGGGATTACACGCACCTGCCACCATTCCCAG
 CTAATTTTTTTCTTTGTATTTTGTAGTAGAGACGGGGTTTCACCATGTTGG
 CCAGGCTAGTCTCTTTGTTGACTCTTAACCATCCTTCAGTCTCAGACAAA
 ACATCCCTTTCTCAAGGATTGTGATTAGCTTGATTATTTGCTTATCTTTC
 TCCCTGCTAGTCTGTAACTGAGGGTAGGCCACTATATTCATTGTTCTTG
 GCACCAAATAGAACTAAATTAATGTCTTTTGAATGAATAGGGCTTTCTC
 CTTTTAAAGATCCCTTCAATACAGTAACCACTATATATAAGTAGCCAC
 AAGCCCATTCAATAATACTACTAGTNCTTGCGCCAAACC

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GGCTCAGCGTTACTATACTGGTCTCAAACCTCCTGGGCTCAAGCGATCTGC
 CCCCCCTCGGCTTCCCAAGTGTTGGGATTATAGGCGTGAGCCACGGTGCC
 TGGCCTCAAATAACTATTTAAGTGAAACAAACTAGTATGGCACTAATGA
 AAAATGTATAAATCCATAATCGCAGAGGGATTTCACTTACTTCTTTTGA
 TTATGTAAAGGTCAAACAGACAAAAGACAATGACAAAACCTTAATGCAATG

FIG. 3 (31 of 52)

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AACACTTTTGGATTTAATGAACATATATTGGATATGTACCCAAGAATTAGA
GAATACATACTAGTTTTGAGTTTATGCAGAACATTTACAAAAATTTAGTG
GAAGCCTAAATTATAAAAAGTTGCTGTACGTAGAATAACACACAAACCC
CTGAGTCCGGAATTCAAAGCCCTCCACACTCTCCTCTACCTTTGCATCTT
TATCCTCCACCACACTGCAGTGCATACTCTGGGCTACTACTCACTGTTCT
TGATTCAAATTCCATGTTCTGTGTCAGCTCAAATCATTCTCTCTGCCTGGAA
TAAGTACTTTCATACATATTCTGCTATTGAATTCTTGTCTTAGCACCCCAT
CTACTCCAAGACGATGTCCAGTTGGGGTTACTCCCTGTCCCATTTTCTTT
GATTACACTTTTTTTTTTCTACTTCCATTATATTATTGATCACATCTGTGC
CACAGTTTTTGGACTTTGTGTCTGCTTTTACTCTTTTCTAGACCCTGATAG
CTCCTGAAGGGTTGGGTCATTTCTTTTTTATTTGCTCATTCTCATGGCA
CAGTGAGTGCTTAATAAATGGCTATTGACTGAAATTAACTGTATCTAAA
TGGACATATTCCACTTCTGGGCCATTCAATCTTTCTTTCTATTGGAACCA
GGAGATGGGGAACCATAACAAAGGTAAGGTTGTGCCATGTGAAAGAACAT
GGAACCTTCCCCTGAGGGCCAAAAAAGAGCAGGGAAAGGTGCAAAGACAA
AATCTTCCATTTTTTAAACAATGTAAGAATGTGGTCCACCTCATGCTCAGG
TGGGACTTTATCATGACGTTATTTTTTGGGGACTTATAGCTGCATCATTTA
CCCCATATACATTTACCTTTAGTGTAGGGAACTGAGGACAGGAATTTTGT
TGATGCAGACTCTTGCTAATGAGGCTAACACTTGGAGAATTTTTATCATG
CATTCAAGAAGCTTGTTTTACATTTCTTCATTAATACTTTAGTTGGTGGT
TTAGCTTTAGTTGTAGGCTTATCAGATATTTGGAGATATCTTCATAAACG
ATGGCTTTGGTTTTAGAAAGAGTTATTCTGAAGCTACTATTTCTGGCAATA
ATCAAACAGCATGGCCATTTGTTTTGTAAGGCCTTTCCTAGAATATGACG
GTAAAATCTACGTGTGGAAAAATGCTTATTCTTCTGTCTCTATAAATGT
GAATCTAGTTTGTCTTCAAATGAAATCAAGTGATTAAAATGTAGTTTTTC
TAAGAAGATAAATGGAGCAAAGCACTCTGTGTTTCACAGTGTTGGAAATC
ACTCATCCCTCATAAACTGTCCCAACTGATCCTGACTCACATGAATGAA
TTAAAATAAGAGTTAATAACATCAATTTACATTTTTTAAAGACACTTTCCC
ATGTTTTAGACTATTGGTTGGAAAAGCTGGTAGGTGTACAATTTGTGGAG
AGTTGGCTGTTTTTGTCTGTCGTTGTTTGACGTATTTCAAAGCCATATCT
AATTTTGTTCAGAAATGGTCTGAATTCTACAAAAATGTTGAGTTGTGTAG
TGTGGAGAAGTACGGAGCCATTTACTGAAAGGCTGGGGGGAAATGACGAG
ACCCTGAGATAAGGCAGTAGTGGTGCGAACAGAGTGGAAGGGAGGTAGTT
GAGATATGTTTCAGAGTAGAATCAGAATGGACATAGTGAACAACTGGATGC
AGGTGGGGGCTGAGGAAGCAAAGTTGAGGATAATTCTGAGACTTCTAGGT
TGATCCACTGAAGTTACATTATTCAACACCACAAGGAACTAGGGGAATG
AGAAGGCATACTGGTTTGCTTTGGAGTGGAAAGGGCAGTGATGTAAGAGGA
GTTAATGAGTTAAAGTTTGGATATGCCTGAACTTCAATTTGATATGTGCA
TCTGATATAACCCTTGGGGTGACCCTCCAGGCAATGGTTGAACATGTGTAT
TTCTTAGTAAGTATAGGCATCACAGACTCACATCAGTAAGGAAGCAACA
GCAAACCTTGATTGGACGATATACCTGGAACCTCAGTACCCTATGACTGGAG
CAAGTCTCTGTGTCAGTGAAATGAGGATAAGAAGAATCTTGACCTTGTGGAA
TATGTTGTTAGGAATATATGTGATGAACAACATAGGATACTTCCTACAGG
GCTCCACATGTAGTAAGGGCTTTATAAATGCTTGATAAATATTATTGTTG
TAATTTATTTCCAAAGTAAGATGCCACTGGAGGAATCTTTGGAACCCAAA
TTAATAACAAATAGGACTGGATGCAATGGCTCACACCTGTAATCCCAGCA
CTTTGGAAGGCCAAGGCAGGAGGATCTCTTGAGCCCAGAAATTCAGACC
AGCCTGGGTGACACAGGGAGACCTTGTATCTATGAAGAATTAAAAAAAAT
TAACCAGATGTGGTGGTGCACGCCTATAGTCCCTGCTGCTTGAGAGGCTG
AGGTGGGAGGATTGCTTGAGCCCATGAGGTTGAGGCTGCAGTGAGCCATA
ATTGTGCCACCACACTCCAGACTGGGTGACAGAGTGAGACCCTATCTCAA
ATAAATAAATAAATAAATAAATAAATAAGTACAAACCAGCAAACACTAAT
CCTTTCTAGAGATTATTGAACTCTGGAGGGCAGATCTGAATGGAGCCAGC
AGAGGGACCTATGGAGATCAGCCTGGCCCTGGACAGCACCAGGCAATGGG
GTTGCTAGAGAGGTAATGGGGTTGAACAGGGTTTAAGCCATGAGGTCTCA
AGAATCCGTGAAGACTCAGACTAATTTTTTTTTTTTTTGCATGAGGATTAG
GTGTTCTAGGAATTTCAATGAGAGCAGGGTTAATGAAGGAATGCAGGGT
AGGAGAGCTGAGGGAAGGCATCTGAGAGAGCCTGGCTTATGAATGGCTGC
GTCAGTATGGCTCACCTGCTTTCCTTGTATCTACTTAGCAGATGATCCCA
CCCCAGGCCTCCAGGGCCAAGGTCATTTCCACATAGTCATGGGCCCTTGA

FIG. 3 (32 of 52)

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GGGCCTGGAGCAGTGTAAGGAAGACAGAGTCTTAAGAAATTGCATTAAAC.
GTCATGGTGCTTGGCAAGTGTGTCATCCTATGCCAAGCCTGATCTGAAG
GGGTGCATGCTCATAGGTAGCTGCTGCCCAAGATTACAGCAGCTTCTTCA
ATCCCAGATCCATGCTCTCCTATATTTCATTTTTTCCAGGGGTTCTGTCT
TCGACAGTGATGAGATGCAGAATGACTTATTGAGTTATTCTCCTGATAGT
TGCCAACTTTTCCAAATGACAATGGGGCATGGAGCTTGAGAGTGGAAATG
AGGCCCTAGGGATAGCGTGCTTAGGAAAACACTCCCAGCCTGATGTAATT
CTGGGGGTACAATGGCATTTCATCATCAAGACTGATGTAAAGGGTGACT
AGCAGTGAGTTGGGGGTGACTCGCACTGGGGCTAGGTTTCTGATTCTGCC
TAATCCAGACAGAGCAGAAGCACTAGTGGGCTGGTAGAGGGCCTCCAGGG
CCTCACTTAATGTCCTGGAAAAACAGCTCCAGATTGTTGGTTCACGTTCT
GAGGACAAGCTTGGGTACTACAGGATAGAGAGAGTGGTGGGAGATGCCGT
GGCCTGCCCTGCTGATGCCCTGCCCTGCCATTCTGCGTGTGATGTCTCTG
GGGCATCTTGCCCTTCCCTGCCCAGACCTGTAGTTCAGCTGAGGGCATGTG
GAGGCCAAATGGCTTCTTAGAGTGTTACTTTCCTTGAACAGCTCTGCTGG
GAGAACTGGAGGAGCTAGCTAGTCACGGTAACTGCAGCAGTCAAAGGATC
GTCCCGGTGGAGGTGGGGTGGAAAGGTAGAGAAAGAGAACATATAGCGTT
TTCCTTGGAGATGTGTGGGCATGTCATAGAGGAAATACCCAATTCTGAG
CCTTGAGCCCTCCAGGAAACCTTGGAATATTAGGTTAGTCATCCCCAAGG
AAGTCTAAGAATTCTGGTCTCACCCTCTCCTTTAATTCCCACAATGATC
CTACATGATATTAAGGAACACGGGCCAGTAACCCCTCCAAGCAATGGATGT
GGTGGTGAAGTTTGACCTCATGATGGAGCGGAGGTTGGTTTGAAACCTAA
GAATTTAATTTATTGTTTCAAACGTCTTCCACTCAGCGTTATTAAAGCA
TACATAATTGACACATAAAAATTGTATATGTCTACGGTGTACAATGTGAT
GTTTCGATCTATGTATACATTGTGAAATGATTACAACAAGCTAAATAACA
TACCCATTTCATCGTGTTCAAAGGAATTAACTCAAGCACAAAAGAGAGG
TGCTGTTGAAGAGTAGGGCTGCTCTATCTAAGTAGTATGTCTGGGGTGT
CCTGGATCAGGGTCCTTTTGTGCTAGTAATAAACCAGCCCTTCTGGGGCT
GCTCCACTTTCCCCACATTTTCTTCTGGAGCCTCCCTAAGAATTAGGACA
TGGCCACTTTCTCTGCATAGGCTTCCTACTTCAACAAGGACAGGGCTTGT
GCTGCCCCATGCCACTTGAGTGTCCCTACAGCACAGAGCTGAGTGCACAC
TGGCTGAGTGAGGAAATCCCCCAGATTAATCTTGGTTCTAAGCATCATGG
CTGTATTTACACGTATATGAATTACAAATTACAGCATAGTCGAATAAGG
ATTTTTGTGCTACAACCTGGAATCCCAGATTATGCAAATTGGATAGTATAA
TATTGAAATTCCTAGGACTTTTTTATTAGTTTTTAAAAAATTATACAAGCTT
AGAGTAAGAAATTAAACAGTGCAAAAGAATTCAGTGTGAAAAGTAAATG
CTCTGTCTCTGCTGAGAGACAGATATTGCAGCCCAGATACTACTGGGGTC
AATAGTTTTCTTTAAGCATGCCATTTTGATGGTTTATGGGACTTACAGCT
CAAGAAGCTTGACACTAGGGTTGATCTCAGAAAATCATTGTTGCAGGTAT
TAGATATGACCGTCTCATAAAGATACACACACAGACACAGCGATTGGAGA
TATTCAGTGGGGCTTATGGGCTGCTTGTCTTTCTGCTCTGTGCCTAAGT
TGGGCTCAGAGTAGCCTGGCATCGGCTGTGGGGAGAATGCTGGCATGGGG
TTAGCAGGAGCCCACTTAACATGTCCTAAGCCACCTGGAAGAGTCCTTCA
AGGAGACCAGACTCCAGAGGCCCTAAGGAAGGAAGGACTTTTGCCCGTTT
TTAGGTATTCTAGTCCCAGAGTTTAGGGAGGAATGGTTTGGCTTTGGGTC
GTGTGCCCCCTTTACCGAGTGGGATGGGATGTGCCCATGAGCTGTTGAGCT
GGCTCTTGGAGAAGACAGCAAAGCGGGAATAAGAGGTCAGGAAGCTGTG
TGGTTGTAGGAAATCCCAGCAGAGGGCCTGGGGGTCAAAGTGGTCATGG
TAGTGACGGTGGAGGCTGAGGTGGTAGAAAATCAGAGGACAAACCCCATG
GGCTGCTGGTGATCTGACCGAGCTCCTATGCTCTCCTGGTTCATTTTAGG
CTCTGTAGCAGCAGATGATTGGCTGGTGTGAGAGCAGTGCACCTGCCATA
TCAGGCAATCCAAGACAAGTCCAAGCTACGCTGGGAGGAAACCTGAAGGC
AGCAGCAGGTAGACTGGCTGAAGACAGACAGGCAGGCAACTTGTCAATCA
GATTTGTGTTTTTAAGGACTTTTAACTGGGGAGCCCTCCGGGACAGATCA
GATGAGAGTGAAATGTGCTCCGCCTTAGCC

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GGCCGTTTCGCAATTCTGTAAAAGGGAGAGTGGTTTTATTTATTTTAAAC
ATAGTCAAGCTGCTAAAGTATATGATATGTATAGATAGAGTATAATTAA
TACTTTCAACTACAGACAAAATCAGGAGAATGGAATTAAAAACAATTTA
CAAATGGGTAAATGGCAGCATTGGGTTGCGCCCAACCACGAGAAGGCAGAC

FIG. 3 (33 of 52)

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ACCAAGATTCTAAGATC...ACGTGGCCAGCACTTCAGACTTCAAATAGA...
TTCGTGATTATGCATTATTTTTCTCGGAAAGTTTTCACTTCACTATATGC
TACTTGACACTTGCTTTTCTTAAGACATCCCTCTATTTTTTGAGATGACTAA
CTCAGCAATTCATTTCTCTCACGCATAAGCTGTCACTCAACCCAAACCCA
CCAAGCCTGCATTCTACCCCTCAATAAGGTCTTGGTGTGTAACTGACCCA
CTTCACCTAGTTCCCTTAGCCCTCTCTTGACCAGACATGACTCTTTCATAA
GCTAGACCTATAAAGTCAGGGCTCTTAAGTAGCTGATCTCTGATAGTGCC
AAGTGTCCCCCACTGTTTACATTTTCCACTCCAGCTTCTAACAGGTGATA
GACTGCTTTTTTGGGGGTAGGGGCACCAAAACATATAGACCTCATGTTTGG
ATGTAGACACTCCAGTTTCTTTAAATTACAACACTACATATTAATAATGACT
TCCAAGTGATACATTTTCAAGTCCAGATCTCTCCCTGGATCCCCAAACTTTGT
AAAACCCACCGCCTAGTTGATATCTTTTGATGTCTGACAGGCATTTCAAA
TTTAATACTGTCAAAACAAAGTTATTGATTTTTCATCTCTGCATCTGTTA
CAAATTTTTCTTACTTTTGGTAAATAGCACCCCAGGCTGTGTCACTGCCAA
GAACTTTCCACAGCTCTTGGGAATAAAATTCAAAATATTTTTCCAAGGCAGA
AAGGCACAGTGTAATCTGGCTCCTGCCTACCTCTCCAACCTCGTATCACA
CTAGTCTCCCTGTCACTCACCCCTCCAGGAGCTCAGGTATCCTTAAAGT
TTCTTTTCTTTTTTTTTTTTTTTTTTTTTTTTTTTTGAACAGTTTTTGCTCTGTT
GCCCAGGCTGGAGTGAAGTGGCATGATCTCAGGTCACTGCAACCTCCGCC
TCCTGGGTTCAGTGATTCTTGTGCCTCAGCCTCCCAAGTAGCTGCAATT
ACAGGCGCGTGCCACCACACCCGGCTAATTTTTGTATTTTTTAGTAGAGAT
GGGGTTTCACAATGTTGGCTAAACCGGTCTCAAACCTCCTGACCTCAAGTG
ATCTGACCACTTCAGCCTCCCAAGGTGCTGGGATTACAGGCGTGAACCAT
TGTACCCTGCCTCCTTGAAGTTTCTTGATCCAGACTCATTCCCTGCCTTAA
GGTCTTGCATCTTCAGTCTCCTCCCTCAAATGACACCTCCATGAAGACGCA
ATTACCTGTAATTACCGTGTCTTATTTAGTCAATGTGTTGGTTTTCTGTC
TCCTCCACTACAGTGTAAGCTCTATGAAGGCAGAAACCTTGGCAGTCCAG
TTCCCAGCACAGTGCCTAGCACACATAGGTATTTAATAACACACAGTAAA
ATTCACCTTTTAGTGTGCAATTCTGAGTTTTTGACAAATGCATCAAGTCAT
TTAAGTCTGACTATTATCAAGCTATAAGATGGTTGCAACACTATCACTAA
TTCCCTCATGCTCCTTGGTAGTCAGTCTCACCCCTAACGCCCCCCTCCTG
GCAATCACTGATCCGTTTTTTGTCTTTATAGTTTTTGGTTTTTCCAGAATG
CCAATAACTAAGTTTTGAATGAATGAATGCTATTAACCTCTCATTCTGAC
TCCAGAGCAACATCCATGCAATATTTATTATTTTCAAGCCCAAATACTGCC
CCCTCACCTTCACTCCAACCACCTACTTGATGATACAAGGTGAGACATT
GGCATGTGCTTCCCTCCATGTTCCCTAGCATTTTCCCTATCTCCTTAGCCTT
CCTTCTAATCATAAACGAAGAGTGAACCTTTCCCTTTCTAAAGGCAACTTA
CTCCTAGGACCTCGATGCCATAATTTTGTCTCTAGTACTTTCTATATA
TACACCAAACAATTAGCTCCAGAAAGGTAAAGACTCACTGTGTGCTCATC
ACTGTGTCTCCTAGCGCCTGGCACACTGCAGGTGCTGAAGAAACACCTAC
AGAATGAGTGAATGAATCTCTCCCTCTCTAGACTCCTTCTCTTTTGTAAT
CAAACATGTTCAACCTGCAACACAGTCTTATGACCAATCCTCTGTTGTCT
GACCTAGGCTGAGCTCCAGGGCTGGGACCCTGACTTCCTTATTCACCACC
TCAAGGTCTCTGCACTCACTTCTCTTTCTGCTCAGGATTGTTTTTCTTCT
TGTCACCAGTCTTTTCTCAGACTTAGGTCTCAGCTCAGACATTGCTGTTG
AAAGTACTTCTACTGATCCTTTTATCTAAAGCAGCCATTCCAGCCCTACT
CTCTTGATCATAGCACCCCTGAATTAAGTTGTTTACTTACTGTCTCTTCAG
GAGGGCAAGGAGCTTGGTGGTGGTGTTCAGGGCTGTACCAAGCTGTACCT
TGCTTCACCCTGCTACACTTTTTTAGCAACCATCTAATTTTACATGCTCCC
TTCACTCGTCAGAAATTTCCCTTATTTTCTACTTCAAGCAGGTATACATAT
GTGCTTCTCCTGGGAGGCTCACCCACTTCATGAGACTACATTTGGTCCTG
GGTAGAAAGTGTAACAAATCCACTGGCTCAGTTTTTAATCAATGTATGTTA
ATATTAACCAACCTGAGATCTTGATTTCCACGCCTGGCTAATTTTGTATT
TTTAGTAAAAACAGGGTTTCTCCATGTTGGTCAAGGCTGGTCTCGAACTCC
CGACCTCAGGTGATCCGCTCACCTCGGCCTCCCAAAGTGCTGGGACTACA
GGCATGAGCCAGCGTGCCCGGCTAAGATCTTGATTTCTACCATCTGAAC
TCTGTATTTGAACTGACTGCTCCTGCTTGAGCTTACTGGCCAAAACCTGG
CCCACTCAGACTCACGGAAGTTTCTGGTTCTTCCCTGGTAACTTTTCTGA
ACTTAACCACTGGTTTGCTTGACAAGAGATTACCATCTTCTCACTTCCTA
GCTATGTGAACCTCACTTATCTGCTCTATTGCTGTTCACTCTAGCACGGCA

CTTATTGAACGAGTGTCTACATCTGCACCCCTACTTCTTACTCATCCAT
TCTGTTTCAATTTCTTAAAAAGAAAAAAGCTATTGTAAACATACG
ATTACAGAAAATGATTTATAACATGTGTATGTACCACCTAGCCCTGTCAA
GTCTTAATATTTGTTATATTTGCTTCAAATCTTTTTTTCAGACTGTAGTTA
AAAATTACTTAGGAGCCATTATTTATGGCCTATTTCTTGACCTAGTCTTC
TTGATGGTCAATTTGCCTAATCATCTTAAGTTGCAAAAGCTTAGAATTAA
AGCAAAGTACCTTCGATCCTCTGCTGTTGCCTTCTTTTAAATATTTGGGT
TTGTTTGGGTCCCATTTACGGTTGTGACATCAGCTTGAGTTTGGGAGCT
GTCTTGTTCAGAAAATGGTTCTGGGGAACAGCCTTTTTCAACTTGGAGTC
CAAAGTCTGTGCTTTTTGCTGAAAGCCATTATTGTTATGTTTATTACCAC
TGGTTCCATTTGGTCTTATGCTAGGGGTGCTTGGAAATGGCTGAATTAAAT
CTGCCAACTGTCAAATTAGGCCTCTGGCTTACGGCTTTTGACTTTTGCAG
TACACATGATGTCTGAGGTATACAACTTGGCTGGACTTCTGATCTTGCT
TGATGTTTGGATGTCTGTTGTTATATTCACCCTGAAGCAAACCTGGGGTAT
GTTCTGGGTTTGGTGTGCTTCACTCTCTGTTTCAGTAACAGGGTATGACCG
TATCTTAGTTTCATTTGGTCTTTTCATATTGACTCCTATTAACCTTTATAT
CTTTGATGTTCTTGACTACTGGTTTCTTTGATGACTGAACTTTACTAAGG
GTCCGAATAAAGTGAGAGGGAACCGTCTTGAGGGTTTTACTCCTGGTCT
TGCAAGATCTGCTCCTCTAGAGAGTTGCTGTGATTTTACTGGGAAAGTCC
TGCTTTGTGTTTCTCCAACAAATTGTTTATTAACCCTATCTTTCAGAACA
GCACTATTAACCTGAACTTTTGCCCAAGGCTTGTTTAGGAACTAACTGTT
CTTGGTTTGAATTATAAGAGTCAGTCTTTGGCTTACTTCTGGTATATAATT
TAGGATCTGGCTTCTCTCAGGTTCTGTTAAGATATCTAGCAAGTTCTCT
TTGTTTGTGTTTCTTTTAGAAAGTTATCCAAAGATTCCTTTTCAACATGGAT
ATTATTCATAAAGTCTATACATTTACCATTTCTTGATCTGTAACTGCT
GCTTTGTAGTTTTCATTTGCTCTATATTAAGTGACCCACAGGTTTTCTT
GACAGTCTCCTGTGGTGGACTATCTAGCTTCACACTGTTGAAAACCTCTT
GCTGAAAAGCTTAGACTATGGGTTAGAAGAAACACATTTTGAAGTCCGCC
TTTTTGCCCAAGTTTTGGTGGCTCTAACTTCAGCTTCTGGGACCTGCA
GTATTAGGTGGTCTGGGCTGGAGTTTAATGCTGATGGACCTTTTAGGTTT
GACAGGCAAAACAACATGGTTGGTAACATCATTTTTTGGGTCTAATAGTCT
GAAAAAACAAGAAAATACATATTAAAAAATCCTTAACATATCTTATTGT
TTTTAAATAAATACTGTGTTTAAACACATGCTAAAAAAAATCATTTTT
AGAATTTTCATCTAAGAAAGTTGAATCCTCAGAAAGTAAAGAAAGACTCAC
TAATAGGTAGTTTTTGTGTTTTTTTTTTTTTTTTTTTGGAGACAGGATC
TTGCTCTGTCACCCAGTCTGGTGTGAGTGATGCAATCTTGGCTCATTGC
AACCTCTGCCTCCTGGGTTGAAGCAATTCCTCCACCCCAACCTCGCAAGT
GGCTGGACTACAGGCGCATGTCACCTACACCTGGCTACTTTTTTGTATTTT
TAGTAAAGTTGGGGTTTCACCATATTGGCCAGGTTGGTCTTGAAATCCTG
ACCTCCAGTGATCCACGCACCTTGGCCTCCCAAAGTGCTGGGATAACAGG
TATGAGCCACCACACCTGTCCTAACAGGTAGTTTTTTACAACCTTGAGTTCC
TATCAGAAGTATATTAGAATCTTTTAGCTTGACAGAATTAAGCAGAGATG
CAGTGAATATACAAAACCTTGCTCTTTCAAAAATGAATTTGCCTCAAACAG
TAGTTGTTGAATGCCTATTATATCCTAAGTGCCCTCCAAAGAACCCTGAA
AAAATACATACATAATGAACTTATGTTAGGGTACCTCCCAACAAATCTCT
CCTAGTACTTTGTATAGCCACACTATATGTTTTTTAAACCACTGCCTTTG
TAAACATCACAGTATCACTCAAGAACCTCTGTCTCATCCCTGGAGATCAG
TGACAAGGAGATAGGTGGCAGATGATGTGAGGCCTGAGATATGCTGCCAC
AGCTCTCAATAAACATGTAACATCTTAATAGTCATATTTGTAAATCAGC
CAGGACAGGGTTTTAAGGTTAGAGTCTATGTTAATAATAAACAAATGTTT
AGTCATGTGATTTAAGTTTGGATAAGAAAGGTAGGACTCGATTACAGAGA
ATTTTGAAAACCTAGGGAAGGGAGTTTAGAATTCATATGGTAAGTAATTGG
GCAAGCCACTATGAATTCCTGAGCATCTCTCATGAAAGCAATTACTCAGA
AAGGAGAATTTACAGAGATTTATGGAATATGTTTCCAGGGTAAGATATG
GGAATGCTAGAGTTACCACTCTATTTTTTGATTTGACAAATATTGTGAAGA
ATCACTACATAAACTTGGCGAGTATGTAAAGGATTTCTAACCAGAACCAT
TTGGCATTGAGGGCAAAGAAATGTCTACTCTGGATGATAGCGGTGTGTGT
GGTGTACTAGGAGTGAAACAGCGGAGTTGGGAGTGGGAGGCAGAGAGAT
GGATGGTATACCCACAATGGCTATATCTGGATTAATCTTTGAGCACCAAC
ATTTATATACACCTCGGATCTCTCCATCATTGCTTACTGAAGAGGTGGAG

FIG. 3 (35 of 52)

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GGACGTTGGCATGAAAGCCTCCAAATGTGTTTTTTTAGTTGCTTTCTTA
ATATTAAAAACGAATTGATATAATCCACAAACCATAAAATTACCATTTTT
AGTAAGTGCACACTTCTGTGGATTTTAGTATAGCCACACTATTATACAGC
AATCACCACCTGTCTAATTCAGAACATATTCATCACCCCTAGAAAGAGAC
TTGGGTTTACTTGTGTCAGTCCCTCCCCA

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GGTCTACATGTGCTCGCAAGATTGGATATTGAAATATCAGCAAGAAATTA
AATGACATAGTAGTCATTATGCCTAAATTATTGTTATTTTTTGATTGAAA
AAAGTTGAATATTTCAAATATCAAGGTAGTAGTGAGATATAATAAGAGA
GAGTCAGTTCTAAGTATAGAATTGCTGATTAGCTTAAGCTCTGTTCTCCA
ACATTTGGGCCACATTGAAGAGACCATGTAGCTGCTTTCAGCCTCGGTTT
CCTCCTTTGCAAAATGGGGATTACACTACCTGCCTCACAGAGATGTAAAC
TTATGACATGTTATCATGATTGCCAGGGGCCACCTGTTTTCTTTTAAACA
TTGAAATCACTGTGCCTGAAACAGGGATTTCCTGCCCCTTTGTGCAAGCT
CCAGAAACAGGAGTCAGCCTGAGTCCCGCAGCTAAGAACGTGGATTCTGG
TCATTTTCTCATAGCGAACACACTTCACAGGTCTTCAAGGGAGTACATT
TTCCTATAACTCACCTTAATCTCAGTTGAAGCCTCGTTTCTTATTTTGCA
CTGTGGCCAAAACCTAAATCTCATTTCTTTCACGTAAACTTCAGCAATTC
AATAATAGTACAGTCATTTTATGTTTCAACTGAACCAAGTCAGGGTTCCA
CTCCTGCCTCCCCTTTCTGCTCTGAGGACATCCATGAAGTGGAGGGGGTC
TATGTAGCCTGGAGCTATTGGTGAGGGGGCGATGGGTCCGTGGTGGTCTTG
GGGAAC TGCGGGGCTGTGTCTGGCTGGTCTGGTGTCTGGTGATTGGCCTT
GTTCCACGCGGTTACGCTGCAGGACAGTTTCGTGTCCTTCTTGTCCTAAT
GATCAGCTTTTAGGCTCACGGGCTGTCTCTGCTGAGATATGGAATAGGA
CAGCCTCTGGATCTTCTTTAACTCTCCTGGGGCCACAGGGGACTCTGTT
TGTGTCTGTGCCCCACATAGGATGATTCTGCCACAGCCTTTGCTGCCATTT
CTTGCTGTTCTGCTGTTTTTAGTCTCTGGAGGGCTTGCAGTTTCCTTGGG
GTCCCTGTGGAAGCAAAGCAAAGTCCTCTCCACGCTCAGATGTCTAAACG
TATCTGGGTTTTATCGTCCACCCATCCAGAGCTCAGTCTAGAGGAGGGG
GCAGCCTTCGGGTTCTCTCCTTCCCTCCAGAGCCTCTTCTTTGCACCAG
GGCAGCCTCTTCTATCTGTTGGAAAGGGCTGTCTGGTTCTTGAATATAG
AGTTGCAGGTTTGAGGGGTGTAGGCTGAGGTAAGGCAAACCTATCACATGG
AATAAAAATTACCCTGTGTCAAGGAACAACCAGAGCTGGACAGTTTTTAA
ATGTGAAAACCAATTTTATTCAGGACTATGGCGAGAGGTGAAGTAAGACC
TCAGTATAGAACTGGGCTCAATTCCGAATGCAGCATGGGCAAATGGGAAT
GTATAGCCTAGGAGCAGGGTGGGAACCTGTGGATGAAGAATTACTAAAAG
GGCATATCAGGGGTGAGGGGGCGTCCCTGGCTACACCCACTAACTACTGTT
GCTGAAGAAAGGCTGGTGACATCACTGGGGAATGGTGGGGGATGAAGAA
TCCAATCAGATGGATATTGAGGATAAGGGGATCTTGATAAACTGGCTTAG
GAGGGTTTTTGCTAAACTGGTTTTTCATAGGTAAAGTCCACAGACAGGTCT
TGGAGAAAGTTCAGGGACCTACGGTTTTGTTCCGGGCAGATGCTTTGTCATC
TGTCACACTGGCACTGTCACCTGGCTTTCTCTTTAGTCCCTCCCCCTTT
TTTTTTTTCTGGAGTAGTTTTGGGAGACCAGAGGAGCAGGGAGTTAGGGAG
AGTAGTCAGAAAAGGCCAGAGAAAATAAGGAGGTGTCTGTAGGGAAAATC
CTTAAATCCTCTAATTAAATTAATTTAATTTATTTATCTGGGACAAGGTC
TCACTCTGTTGCCAGGCTGAAGTGCAGTGGTGTGATCTCGGCTCACTGC
AGCCTCGACCTCAGGGCTCAAGCAGTTTTTGCCACCTCAGCCTCCTGAGTA
GCTGGGGCTCACAGGTGTGCACTACCATGCCCGGGTAATTTTTGGGTTTT
TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGTAGAGATGAGGTTTCGCCATG
TTGCCCAGGCTTGGTCTCGAACTCCTAAGTGATCCATCCACGTCGACCTC
CCAAAGTGCTGAGATTACAGGCATGAGCCACTGTGCCCGGCCTAAATTCT
CCAATTTTTTAAATGCTTCCCTGTTCCCTGTTCCAGATTTGGGATATTGAC
TGCTGTTAAATCAGCGATTTCTCCCTGTGGAGAGGTAGCCAATAGGAAGC
ACAAGAGTGAGGAGTCCTTATATCGAAATAGAGGGTAAGAGAAGAGACA
GATGTTATCTTGGCAGTGATTAAAGAACAGCGAGTCTGTAAGCAAAGCAA
AGCAAGGCTCCCAGGTGCTGAGAAACAATGGCTTTCTGGGGAAGCGTCTG
TGTTCAAGACCTTAAGTTGGAAACATCTCTGAAGATGTTTGCCATGAAGG
TTTTCTTCTGAAGTTGAGTCTTTCATCACTAGGTAGGCGTGTGTTTGGAGT
CTCTATCAAACAGATCCTGTGTTTTATTAGGAAGCTGTGGTTTCATAAGCC
CCATGCTAATTTTGCAAGGTAGCAGGGTGGCCCTGGCCTGACCCGGGGACA

FIG. 3 (36 of 52)

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GAGTGGCTGTCTCCCTCCCTCCAGGCAGGAACTCTCTCCTGCCACCTAGTCTCTCTG
CTGCATACCCACATTTCAAGGGAGCTTCTGGGTGGTGGAGTTTACCAGACT
ATGGTCTGAGGTAGAGTTAAGCAAAACAAACTAACTGCATAAAGAAAC
AGAAAGAAAATCAGGTGTTATAAAAAACAATTTGGCATTGTGTTGTGTTTC
AGCTCCGTGTGATTTATTGCTTCCACAAATAGTGCCGATATGCACCAGG
CACTGTTGTAAAACCTGAAAATATGTTTTTTGGATGTGCCCAGTCTGTGAGT
ATTAAACGATGGTTGATTTGAAATTTGCTATGATTCATATTTCTGGGGGT
AAGATGCAGGATTTCTTTGGGGGGCCTACGATGTGGCATTCTAGAATTCT
CAAAGAATCAACCCTGGTGGGACCAGGAAGAGCTGAGCTGAGGCCTCTCT
GCTCATGTGTACTTACTGGAGATCATGGAGACAGGTGAGCCTGAGTGCAC
GTCTCACCAAAGCCACAGCAGAGGGGGAGGAGGCGGAAAGAGAGCTCTCT
CCATTTCTGAGAAGTTAATGGTAACAATGGCATAACATACCTACTTTACAG
TTGAAATTGGAAACCACAGCATTAAAGTGTTCCTCAATGAAATTTGGCAATT
TGGGAGTTTTCTGAGCTGCATTGGATGTGGTTTTGCATGCTGTTAGGATG
AGCAAGAGATGATGGAGAACATCTTCCTTTTGAGCTTCCTCTTGACGTG
GGTCACTCCCACTCATGGAATTAGAAAGCTTAGACCTAGACTTGAATCTC
ACCTTCTCAAGGTGCTCCCGGGCAAATCACTTAAGATCCATCTTCTTCTC
CTCCTGCTCCTTCTCCTCCTTCTGAGTTTTTTTTTTTTCTTTCCAAAATTC
AAATGACACGGTACTGGTAGAAGAAAAGGTCCAAGTCTGCTTTTACAGCT
CCCCTCATCCCCAAATGTACTCCGACCCCAAGATGACCATGTTATCATTT
GATTGACATCCTTCTAGTTTCAACTCATTTCTTTGCATGTATATGCACGT
ACATATACACTATTTTATTTTGGCAGGGGTACCGTTTAGCTGCATTAAT
TTCTTATAAAATAATCTATATTTACTTATGGTTTACGTAAAACAACATAC
ACATGTAAGTGTATAGCTTGATAAGTCTTCACTGTAAACCAAAAATAAAA
TTCGAAGCCCCCCCCAACCGTCTGAATGGACCCCTCTTCTTGCCCAAGAGC
ATTCCAAAGTTAACCTGAAAAAACTAGTTCAGGTGATGGAAGGGAAG
GTTGGACATGCCCCAGTATACCCTTCTCCCTTTTGGAATTCAGGAAAAGC
TGACCAGCATTAACATCAACACAGACCTTATGTCTGATAGGAACTTTGA
CAATCTATTCCCTCTGAAGCTTGCTACCCGGAGGCTTCATCTACAAGATA
AAACCTTGGTCTCCACAACCGCTTATCATAACCCAGACATTCCTTTCTGT
TGAGAATAATTTACCTTGTAACCTGGAAGCTCCCTGCTTCAAGTTCCCTC
ACCTTTCCAGATTGAACCAATGTAAACCTTACATGCATTGATTGATGTAT
TATGTCTCCCTAAGATGAATAAAAGCAAGCTGTATGTTGACTGCCTTCAG
CACAGGTGTGTCAGGACCTCCTGAGGCTGGGTACCGGATGCATCCTTAACC
TTGGCAAAATAAACTGTCTAGATTGACTGAGACCTATCTCAGATACTGTT
GGGTTCAAATATATACTTATGAACTAATACACAAATCAAGTCATAGAA
TATTTCCATCACTCCTCATCTACCCCCAAATTTCTTATGCGTCTTTGCA
GTCAACCTCCCACCCCATCCCCAGGCAACTGCAGATCTACTTTTTGTCTC
TGCACCTTCAACTGACCCTTTCTGTGATTTTCATATGAATGGAATCATGCG
CTGAGCAGTCTTTTGTGTCTGGCTTCTTTTGCTCAGCATAATGTTTTTGA
GGTTTGTCCATGTTTTTGTGTTTGTCAATGGTTAATTTCTCTCCATTGCA
GAGTAGTTTTCTATTGTACATGTGTACCACAATTTGTATATCCATTCCAT
TGCTGATGGACATTTGATTTGTTTCCAGATTTTGGCAATTATGAATAGAG
CTACCATGAACACCCAGGTACAAGTCTTTGTGTGGACTTATGTTTTTCATT
TCTCTTGGAATGGAACCTGTCAATCAATAAGTATATGTTTAACTTTGTAA
GAACTGACAACAAATTATCTGCGATGGTTATGCCATTTTGTTTTTCTAC
CAGCAATACACGAGCATTTGAGTTGCTCCACAACCTTTGCCAAAACCTGTT
TTCTTTAATTTGGACATTTAAGTGGTGTACAGAGGCATCTCATTGTGGTT
CTAGTTTTCTTTGCCCTGATGACCAATGGTGTGTAACATCTTTTCATGTG
CTTTTTGACCATTTACATATCCTCTTTTGTTGAAGTGTCTGTTCAAATATT
TTTGCCCATTTAAAACATTTGGGGGTTTGTCTTATTATTGTGTTGGGAGA
GTTCCATATTTATTTATTTATTGAGATGGAGTCTCACTCTGTTGCCCAGG
CTAGAGTGCAGTGGCGTGATCTTGGCTCACTGCAACCTCCACTTCCTGGG
TTCAAGCAATTCTCCTGCCTTAGCCTCCTGAGTAGCTGGGATTACAGGCA
TGTGCCACCACACTGGCTAAGTTTTTTGTATTTTATGATAGAGATGGGGTTT
CATCATGTTGGCCAGACTGGTCGCAAATTCCTGACCTCAAGCAATCCACC
TGCTTCGGCCCTACAAAGTGCTGGGATTACAAGCATGAGCCACTGTGCCT
GGCCCATATTTATTTTTTATTCTTTATTTTGTATACAAGTTCTTGGTCAG
ATACAATAACCTGGTCAGATGAGATAATGAGTTGGAAAATGCTTTGCA
AATGGGGGAGAATAATTTAAATGTTATTTATTTATTAAGAGCAGAGGCC

FIG. 3 (37 of 52)

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TTCTGTGCGGTGAC...AAGCCGTTTGCTTCTTCTGCCTTTTATAAA...
AGCAGAGTCGAGCTACACAGGCTGTCTGTGTTGGCTGCTATTAGTTAATC
AGAGAGTTTTTTTTTTCTTGCCTTGTCATTCTAATTTGTGACACATAATT
AGCCACAATATGTGTTTTTCAGTTGTGACACTGGCCTGGGAAACCAAGGGA
TGTTTAGAGTGGATTTCCTTGATTTTGCAATAATTGTGTGTTTTCTGCA
TCTTCTGTAAACACAAATTCATGGAAGCAAAACATGGAAGCAAAGTACC
CTGGACATCCCCCTTCTTTATGAAATTGATTTCTCTTAAATGTAATGTT
TGCTTGTTCCTTACTTTAAAGCAATTTAAGAGTTTATTGAGAAAGTGA
GCCCTGGAAACATAGATGCATAGAGAGAAAATTCTACCACCCTCAGGTCC
CTATTGTCTTCTCTCATAAAGTGTAGTTTCAGGGCCTTTTAGAAGTTTCT
TTTCTGCTCTGATTTGCATGTTTGTGAGTGTGCTATTTTAAGTATTTGG
ATTTGGTCTGCAAATCCTATGAGAGATGGCAACAGAGTAGGGATCTCAA
GCCTGCAGGTGTATTAAGTCCAGCAGGGCCTTGATTTACAACAGAGGG
TCCTTGAAGACATTCCATATATTATGCTAGGGGAGTGGCCAAGCAAACCT
TAATGTGTCCCTATGGTGGGATATTTGGGGTTAATACCTGCCCTTCTCTT
AATTTCTTTTTCTTTTCTTTTTTCTTTTTCTTTCTTTTTTTTTTTGAAA
TGAGTCTTGCTTTGTCAACCANGCTGGATTGGAGTGCAGTGGTATGATC
TCAGCTCACTGCAACCTCCACCTCCTGGGTTCAGCAATTCTCCTGCCTC
AGCCTCCCAAGTAGCTGGGACTATAGGCACACACCACCATGCCTGGCTAG
TTTTTTTTTTTTTTTTTTGAAACNGAATCTCGCTCTGTGCGCCAGGCGGGA
CTGCGGACTGCAGTGGCGCAATCTCGG

>Cont:39

CGCTCGCATCCCTCATATCCATGAGTGTCTGTGGGCCCTGCCTCTGAAA
TAAATCCTGCCTTTGTCTCCAGTTCCTCCAGCCACCCATCCTGGGGCT
GCACCCTCCTCCTTCCAAGCCCTCTCCCTTTCTTCTCCTGGTGCTGCCTGT
CATGTCAAGCATATGCATCAGTGCGACCAGGACATTTGAAATGCAACCAG
TACAATTGGGCGCGGTTATGCCTACCAGTTTTCTTCTTAAACATTTTA
TATTTATGTTTGAAAGCATGCCACCTTTCTTCACTTGCCAACCTTGACAGA
TTTATTAGTTGACAACATCCGCTGATAGCATCAGTAATAAGTTAATTGTT
TTTGCACATGTAGCTTTAATTATTCTCATTATCATTATAGGAGTTATTC
TTTGTAAGGGTAACTGAGTTTTCCAAAACAAACAGAAATTTGGGGTGGG
CCCATGGAGCGTGACTCATGAAATCAGATTCTTAGAAGGACCTCGGCAAG
TCTCTGGGTTGCTGTTAATGAGCCTGGCTGGCTGCCAGGGGTGTGTCTGC
CCTTTATGAGGCCACCACTGTTCAAATGCTTGCCTGCAGCATTACTTGCC
TAGGTAGTGCTTGTTTCTACTGAACTGTCAGGGATCCAATTCTTTGTGGT
CTAAGTAACAATACTCAGATTCACAAGGAATTGATTAATAAGCCAGAATG
CCAATGTATTACATTTTTGATGAAGACCATATTTACAGTGATTGTATCTG
CTCAAGCTCAAATTAGGATTAGAGTTCTGACAAATACATATGTGAGAAGT
ATGAGGTTAAATACTTGAAATTTGGACTTTTCTAGAAAATCTGAATGTGA
TTGCCATTACATACCTTTCTGGGGATGATGATTCTTGTACTTTTATTTT
AAAAGACATAGAAAATACTTAAGAATCAGATTGCTTGGCTGGGCACAG
TGGCTCATGCCTGTAATGCCAGCACTTTGGGAGGCCAAGGTGAGTGGATT
GCTTGAGCTCAGGAGTTTGAGATCAGCCTGGGCAACATGGTGAAATCCCA
TCTCTACCAAAAATACAAAAAAACAACCAAAAAGAATAAA
TTAGCTAGGTGTGATGGTGCGTGCTTGTAGTTCCAGCTACTTGGGAGGAT
GAGGTGGAAGAATTGCTTGAGCCCAGGAGGTGGAGGTTTCAGTGAGCTGG
GGTTGCAACAGTGTACTCCAGCCTGGGCGATAGAGTGAGACTCCGTCTCA
AAAAAAAATAATCAGATTGCTTTATTGCTGGTTTTCTTTCTAAACTGA
GATTGGGTCCCATCATCCCCCTGGCCCCCATTTGGTTAATGGTTCCTCCTTT
GTCTATTGAATAAAATACAGATGTCTGCTTTTGGCAACATGGTTGAATGT
AGACACTGCAGGGTCTTCCTGACTCAAATGAGTAAGGCTTAGATAAAAC
ACATTTTGAAATGCATTTCTGGATGAACAGCAAGGAAAGGAGATCTCTTA
AAATCCTCTTTCTGTTCCCTCTCCCTACCCCTCCAAGTGGGCTTAAGT
AGGAAGGGTGGTGAGCGGCAGGTAAACACACGTCAAAGGCAGTCTTCCTC
TCTGAGGGAAAACACTTGATAAGCATTGCAATCAATGGGCCTCTTTAAT
TATGTGCCAGTGGCAAGAGCGGGTGCTGAACCCAGGGGCCTGCCTCAATC
CGGGGCCTTTGAGGCAGAATAAAGTGGTCTCAGGTTGTTGGCATTTCCTT
GCCCTTCCACCCGAAGCAGACACAAATCCTCTCTGGAGGCAAGTTCCCCA
ATTCAGCCAGTACAACCTCCACAGACTAAGATCAATCATGTACAAGCTCA
CAGACAAAGGTCACCAACACACAGAGCAATAAACAAATTCATGAGTGAC

GTGAATGAGAATAAACAC...AACAATAACCACCAGCTGGGATGCTCTAAG...
CTTCAGCTGTTAGAATTCTCTGAATATAGAATAAAACTGCCACAATGGCAA
ACATGCATCTAGTACTTACTGTGTGCTGGGTTCTAAGAATTTTGCACATT
GTGCCAGATACCGACTCAGCTTCACACTCACCTCCTACTGTGCCCTCTT
AATTTGCACTAGATTAAAAGGTAGAAAGGAAGAGGCAGCTATTCTGTTCT
TGGCTGTGCCTCTGGCAGCACATGCAAAATGGGCAGTAACAGTGGCAGTC
ACAGGTAAGTAGCCTTCTCACAGTGTGGAGTTAAAGGCATGGGACTGAGA
CGAGCAAGGTTCTTAAAGGGACAGTGGCCAGTAGATGACCAGGGGCTACT
GGAGTGGCTGCATGGCTCTGTGGAAGCTCAGAGGAGCCTTGGGTCTTGCA
GGTGCAGTAGCAGCTTTCTGTAGTTCTGATCTCTGGGTCCCACAATCTT
CCCCGTTTTTGTCTCTCCACTTCTAATTTTGTAACTGACTTCCCTGTGTG
TACTTCTCTCTCTGATTGAAATAGCCAGACTGGTTTCTGTTTCTTGATAA
GACATTGTCTGGTACGAACACAGTAACTCATTTAATCCGATATCTCTATG
AAGGAGGTACAATAATTATTTCTATTTTACAGATGAGGAAACACAGCAGA
GAAATAAAGTCAATTGTCTAAGGTTGCACATTTAGTCAAGGGAAGGGTTG
ATATAACATATAATTATTTAGAAAACATCTAAGGAAATAAAAGGCATAAT
TTAAAAATAAACTAGGCAGGTTTAAAAAAATGAAGTAATCTATAAGTAA
AAAAGTATAATTGTTGAAATACATATCTTAGTGGATGGGTAAATAGCTG
AAGAAATGATTAATGAACTGGAAGGTAGTTCTGAGGAAATCAGAATTCAG
CATAGATAGAAAAAATGGGAATTTACAAAAGTACACAGGAATTATAAAAG
AGGTTAAATTATAGGGAGGGTAGAATGAGAATTAACATTGGTCTAACTGG
AATTTTGAAGAAGAGAATAGAGAGAATGAACAAGGCAATATTTAAAGAG
GTGGCTGAGAATTTTTCAGAACCAACACAACTATGACTTTACCAGTAGA
GAAACAATGTACTGAGGAGGATAAATAAATACTATGAACAAATTG
TAATAATAATACTCAACAAAGACAAAGAGAAGATGTTAAAATCAGCAAAA
AAAGAAAGTCAGACTTAGAAAGAAATGACAATGGCAGACTACTCAACAAC
ACAATGGAATCCAAATTCGGTCAAACAGTATTTTCTTCATGCTAGCATA
TAGC

>Contig40

GGGAGTCCGCTATGCTCCTAAAGATTTGCACCTCTGATCTGGTTTGTAGT
TAGTCTCTTTTATTGCTTTATCCTACTCAACTAATTTTTTTTAGTGCCTGT
TTTTTTTTTTTTTAATGTGTGTTGATGACTACAATTCTAACTCATTCTA
CTGATTGATGGGTGCTTTAAATCTGAGCAGTCTTTCGCATTTACTGCCT
GTGATGGCCCATCCCACCAGCTAAAGTGTGTGGCCACTGCTTACAGCACC
ATGTGATAACGAGTAAGGGAGAGATGCCGCCAGACTCTTCTAGGAGCAG
CCAGTAGGACCTTCCAGGGGTTGCAAGCAAACCACAGCAATATGTGGAGT
GTGGCAGAGGATGGCCCCAAGAGGATGTGGCAGCGGCTAGTGCAGCTCAG
CTTAGTCTGAGAGGAAATGCTGGAGAGGAGAGCCCAGTCTGTACAGGCAT
GACAGCCACAAGGACTTCAACAGCTAACATGGCTGAGTGGACTTTATGTG
CTATCTCATTGAGAAAACAGGAGCAATCAGAAAGGAGTCACCTCCTATTT
GTACCCCAAGGAATTGCTAACCTACTTGCATCTGAATGATGTCCATCACTT
CCCTTCATCACCTCCTCTGGGGGCTCTGCAAGGATTTGACTCCTGCATTA
GTGATCTGTCTCACCTACGTTGTGATTACATGAACTTACTAATGTGCTA
TGTGACAACTACCATCTTAAACACAAAAACCTCTTTTGATTCTGTGGCT
CCCTCCAGCTACCCCTGCATTTCTCTGTCCCCCTGCCCCGTCTCTGCACT
CACTTTTATTTTACAGCAAACTACTCAAGGGAGTCTCAGTGCTCCTTGG
CTCCATGTCTCCACCTTTCATTCTCTCCTCAGTTCACCTCCTGTCAGGCTT
CCGTCTCAAGCTCTTCTTCACTTTTGTCTAGGGCCGCTGACATCCTCT
TTCTTGCCAAATTCAGTGGCCAGGTCCTCACTTACTCAACTGCTCAGCAT
TGTTGGGCCTGGTGGACCACATTCTCCTTCACCACCTTTTGCTGCTCTC
TCTTCTCTCCAGATGTTTCTCTCTTCTCACTGGCTACTCCTCTTTTGTCT
CCTTTGTTAGCTCCATTTCTTCTTCCAACCTCACTGTGCTGGTGTGCCC
AGTGCTCAGTTTTTAGCTATTCTCTCTTTTCCAGTGGCATTCAATTAGATG
GTATCATGTGACCCATGGCATTATATGCCCTTCTACATGACAGTTACTCCT
GAATATGAATCTCAGGAAAGATTTGGATTTATTTTAAFTAAATTTTTTA
AATTTTATTTTAAATAAATGAGGTCTCTCTCTGTCAATCCAGGCTGGAGTGT
AGTATTGAGTGATGTGATTATAGCTCACTGCAGCCTTGAACCATGGGCTC
AAGTGATCCTCCTGCCTCAGCTTCTTGAGTAGCTGGGACTACAGGCATGT
GCCACCATGCCTGGATGACTTTTTGTGTGTGTGTGTGTGTGTGGAGACAG
GGTCTTGCTCTATTGCCAGGCTGATCACAACTCCTGGCCTCAAGTGAT

FIG. 3 (39 of 52)

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CCTCTCACCTCAGCCTLCAAAGTGCTGGGATTACAGGTGTGAGACCAJ
CTGGGCTAAGATTCAGATTTTGTATTCAATTGACTGTTTGACATCTTCAC
TTGGACACCTAAGAGGTATCTCAAATATTAATTAACCTTGGCCAAAATACA
GAACCTTTTGACCCCTGCCCCCACAATACTTGCCCTTCCCCAGACTTCTC
CATTTCTGTAAATATCCCCAGTTACTCAACCCTCAAACCTATGAATGCC
CTTTGATTTCTTTCTTTCCCTCATCTCCTACGTTGACGCCATCAGCTAGT
TTTGTGGCCTTTATGCCCAGAATATAATCCTCACCACCTTCTCTCCTATT
GCCCCAGTATAAGATGTCAGTTTTTCTGCACAGTCCATTGCCCTGACCT
CCTGAGTGGTTTGCTTCCACTTTTGACATTTGTATTCTCTTTCCCCCAG
GGTCAATTTTTCACAGCAAGAGTGGCATTTTTTTTTTTTTTTTTTTTTG
AGACGGAGTCTCGCTCTGTGCGCCAGGCCGACTGCGGACTGCAGTGGCG
CAATCTCGGCTCACTGCAAGCTCCGCCTCCCGGGTTCACGCCATTCTCCT
GCCTCAGCCTCCCGAGTAGCTGGGAATACAGGCGCCCGCCACCGCGCCCG
GCTAATTTTTTTGTATTTTGTAGTAGAGACGGGGTTTACCTTGTTAGCCAG
GATGGTCTCGATCTCCTGACCTCATGATCCACCCGCCTCGGCCTCCCAA
GTGCTGGGATTACAGGCGTGAGCCACCGCGCCCGGCCAAGAGTGGCATT
TTAAAACCATATATTAGATCATTGCTTTTGTGTTTGGGAACCTCCAAGGG
CTTTGCATCATATATCAAGTTGACACCTCTCCTACCCAAGCCTGGCTCTT
TCCTGCTCCTCTGTCTCTCAGCCCCCTCCACCCATTGTTTCATGCTGCTTC
AGCCACACTGGCCTTCTTGCCATGCCACATTGTGCTAAGCCACATCCA
ATCTCGGGGCCTTTGCACTCGCATTTCCTCTGCTTGGCATGCTGTACCCC
AGATCTTTCATGATTGGCAGCTTCTGTACATTGAGCCACCTGCTCAAGCC
ACCCTTTCAGAGGGCCTTCCCTGGCCACCTCACCTGAAATAGCACCTCCG
ATTGCACCCATCCGGTTATTCTCCATCCTGTTCTCTTGCTTGGTGATTTT
CCATCACTGATGAGGAAATGAACCATGGAATGCTAGGGCTGATGACCAGA
ACTTTCCCCCACCACCATATTACAGAGGAGGAAATGAGGTCCGAGGT
AAGATGGGCCCAGGATTTCTACTCCCGCCTGGACTGCAGGCACAGCACTG
ACCTCAGCTGTGCTCACTCTTGGCATTACCCCAACCCTTCTATCTCCAAC
TGCCCCATTACCAGAAAGTGAAATGTTCTCAGAGACGGTGAGCCACCTG
ACTTGGACAGCAGCCCAGGGCCCCCTGGCACCTGCTTTCTTCCCTGC
CATCCTTTCTCTCCAAGACCTACCTTTCCCTGTGATTCTTGCCACATG
CTGCATTTTCATGGTTTTATGACCTGATTTCTGAGAGGGATTTGAATTTTC
ATGATTATTTATGTAAGCAAATCATTATGCTTATACAAATGAGAAAAGGA
GTGCTTCTGGACTTCCCAGGGACAAAATCTTGTCACTTGGCTTGCTTTCA
TATTGCTAATTAAGGACCCAGGATGTGGGTGAGATGTGCTAAAAGCTGAG
AGGAGGCTCTGGACTCTGACTATGGGCCCACACCCCTGGGCAGGCATCAC
ACTAGTCCTTTAGGTCATCCTCAACCCAGCTTCCAGTTGAATCAGATGTT
TGTGAATAACTCAGCAAGGCTGTATGGGAAATGAAGAATGAGGTGGGGAA
GAGGCCTGTGCAGAAGACACACTGACTTACCCCTCTACCTCTAACTAGGG
TGTTGTAGCAGCCACCCACCCACCAAGTCTGTCTTCCAGACCACGTATGC
TTTCCTCCACCTTTGCATCTTTTATCTTCTGCCAGCCCAGATGCTTGCTG
ACTCCAGCCCCAAGCCTATAGGATAAGCTACAGCCTGTCCCTACAGACTAC
GCATTGCAGAATCTAAGACATCAAGTCAAGTTCGGAAGCACTTGCCTTCT
CCTCTCCAGGTACACAGGCTCTCCTGGAAAGCTGGTAGCAGCTGTGGAGG
TGTGGTGTGTTACCTGCTGCAGGTGCAGAGAAGTTGACTTCACAGCCCTT
CAGAAAGACTGCCTTCTTCCAGTTGTATTTGTGTACTTGCTTGGGTGTGG
GGAGGATTCTCAGCTTTCTCCACTCAAATTATCAGACCCTTTCCATTTAG
TGGTAGACCATTTCCTCGTCCAGGCCAAGGGCACATAGTACAGAGAAAT
AGGGAGTTGTTACCCAGGGAGAGAACTTGGCTCTAAACCTGTAATAGAAA
GGTCAGTTCTGGTCTGGAGGGTCAATTTTGATCTTTGGCTCAGATCCAGG
AATTGGAACCAAGGCTTTTGAACATTTTAATGCAGGGGATTAAAAAATG
ATACGAGTCATTCACGAATATATTTGCTTAACATCTAAAGAGATCCCTCA
AAACACTAGAAAAAATAAGAACAAAAATCTAATAAAACAAAATTTGTTAA
ACACATTTACCAAATTTTTTTTTTTTGGTAAAAATTCAAATGTCATAAATA
AAGCTAAAGTTCCTCTTGATGACTCGCTCCTCTGCCCTATTCCACTCCAA
GTAACCACTATTATCAGTCTTGCCAATACCCTTCCAGACCTCTCTACCTC
TATATAACCATTAGAAGCACATGGTTTTGCATTGAGGATGTGCAGTGT
GTTTTACGTAAATGTTATCACTCTGTTCTTGTTCCATAATTTGCCTTTTT
CTCTCAATGATTTGCTTGGCTATCTTTCTATTTTCTAGTAGCATCTCCTTTC
TTTTTAACCTTACCATTGTTTATTTAACCTTGCCCTCTATCAACAGATATGT

FIG. 3 (40 of 52)

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AGGTTGTTTCTAGTTGA. TTCATTAAGTATTTATAAACAACGCATCAG1A
GATGTCCATAAATTTCTTTACGGAAGATGGCAAGTAGTGGAATTGCTGAG
CCAAAGAACATGTTTAAAAAACCCTAAAAAACTAGACGCTACCAATTTTC
TCTCCAAAATGGCCATACCCACTTACCCATACAGAGATGATTTGGAATCT
GGCTTCCTCACAAGGTGAGATGCCTTCACAGTTTCATTCTTCCTGGCATG
TCTTCCCTTTTGTATCTGAGAGAGCTGGCAGAATTGTGTCACTAAATCAA
GGATAGAGGGTCAAATGACAGCTCAAGCTCACAGGCACCTCTGCTTTCTT
CCCAGACCACCTGCTTTCTGCCCACAGCTCTGTTCCATCTTATAGAATG
GTTGCCACTTGGGTGTCTGCTCCGACAGCCATGTCATCCTTTGCACTGCA
GTTATGAAGCAGACAGAGCTAGGAGAGGGGCTTTGCCAGCCTCTGCCCTA
GCTTGGAGAATTTCAAAGAAGGAGGGTATTGAGAGTGAGCTGCCGAAGAC
TGGCAGCTCCCTCAACTCAACAGTTGTCCTTCCACAAGAAGTCAGATACA
TTTTTTTGGGATAAAATATTTAAAAATTATTTTATTTCTGAATAATA
TATTTACATGATTCAAAAATCAAACCTGTAGGCCAGGCATGGCTGCTTATG
CCTGTAATCCTAGCAATTTAGGAGGCCGAGGCGGGAGGATCACTTCAGCC
CAGGAGTTCAAGACCAGCCTGGGTAACATAGTGAGACCCTGTATCTACAA
AAATTTAAAAACAAAAATTAGTTGGGCATGGTGGCTGATATGGTTTGGCT
CTGTGACCCAACTCAAACCTCATGTTGAATTTTAATCCTCAATGTTGAGG
GAGGGTCTTGGTGGGAGGTGATTGGATCATGGGGGTGGGTTCTCCCTTGC
TGTTCTCATGATAGTGAGTGAGTTCTCACAAGACCTGGTTATTTGAAAGT
GTGTAGCACCTCCCCCTTCACTCTCTCACTCTCCTGCTCCGCCAFAGTAA
GATGTGTGTGTTTCCCCCTTGCCTTCCGCCATGATTGTAAGTTTCCTGAA
GCCTCCAGCTATGCTTCCTGTACAGCCTGTAGAAGTGTGAATCAGTTAG
ACCTCTTTTCTTCATAAATTACCCAGTCTCAGGTCATTCTTTATAGCAGT
GTGAGAGTGGATGAATATAGTGCCATATGTTTGTATTCCCAGCTACCCAG
GAGGCTGAGGTAAGAGGATTGCTTGAGCCTGGGAGTTTAAGGCTGCAGTG
AGCCATGACTGTACCACTGCTCTCCAGCCTGGGTGACAGCGAGACCTTGT
CTCCAAAAAACCCTGTTGTAATAATGTGTTTATAAAGTGTC
TTGCTCCACACCTGTCCCTATATATCTTATTCCTCAGCCTCCGACAACCT
ACTTTATTCAATTTCTTATGTATCTTCCAGAATCAAAAAAATAATCAA
TACAAGCACAGTGGAATGTATTGCCCTTCTTCCCCCTCCCTTTTGTACAT
CAGAGTTAGCATATCATAAATACGGTCTGCATTTTCTTCTTTTTCAGCTA
TCAGCATGTTTTTGGAGAGGATTTTATATTCTGTGCAGACAGCATGTATTAG
TCAGTCTTGCATTGCTATAAGGAAATACCTGAGACTGCATAATTTATAA
AGAAAAGAGGTTTAATTGGCTCACAGCTTCGCAGGCTGTTCCACAGGAAG
CATGGCAGCATCTGCTTCTGGGGAGGCCTTAGGAAGCTTTTACTCATGCA
GAAGACAAAGCGGGAGTGGATGTCTTATATGGCAGGAGCAGGACTGAGAG
AGAGAGAGAGAGAGAGAAAGGATGCCACATACTTTTAAACAACCAGATCT
TGTGGGAACCTCTGTACGAGAACAGCACCAAGGGATAGTGCTAAACCAT
TCATAAGAACTCCACCCCCATGATCCAATCACCCACACCAGGCCCCACC
TCCAACATCGGGGATTACAATTTGACATGAGATTTGGGCTGGGACACAGA
ACCAACAATAACCAGAGTGCTTTCTCATTCTTTTCTATAGCTGCCTAGTA
TTCTATGTCTTTTACTTTCATTTAGGCAGTCTCTTGTGATAGACACTTGG
GTTACTTCCAATTTTCTTATTACAAATGATGTGCAATGAATAATTTTGA
TCATTTTCCATTTTACATGGGTTATGTCCATCTGTGGGATAAATCTCCAG
GAGTGAAATTGCTGGATCAAAGGGGAAGTGCACTTGTGATTTTCATAGTT
AGCAAATTTGTTCTATAAGGGTCATATCAATTTATAGTCCCACGCGTAA
TATTTAACAGTGGGGATTTCCTGACAGTTTGACCAACAAGGTCTGTTGTT
AAACTTTTGATTTTGTCAATCTGATGGGAAAATACTAGTATCTCAAAGT
GCTTTTAATTTGACTTTCTTATTACAATGTTAAGCATCATTTTACTCTGC
CCAAGATCAAATAGTATTTTCTTTTCTGTGAACAGACTGTTAAGATCCCT
TGCTCTTGTGTTTGTGCTGGATTTTGTCTTTTTTTTCAAATGTTTTGAGG
CAGTTCTTTACATGTGAAACAAGTTATCTCTTTATCTGGGGTGTGAGTTA
CAACTACTTTTCTCTGGCTTGTGTTTGCCTTTGACTTTGCTTCTGGTGA
TTCCCGCAATTCTGAAAGTGACTTTTGCATCATTCATTCTTATACACC
CATGCTCTTGTTCACGCTGGTTCCTCTACCTGAGGGCTTTTCTTTTCTG
CTTCTATCTGGGAACATTTTTTTGAGAGAGAGTCTCACTCTCTCGCCAG
GCTGGAGTAGTGCAATGGCGCGATCTTAGCTCACTGCAACCTCCACCTCC
TGGGTTCAAGCAATTCCTGCTCAGCCTCCCAAGTAGCTGGGATTACA
GGAGCCCACCAAGCCCAGCTAATTTGTTGATTTATTTATTTT

FIG. 3 (41 of 52)

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TGTAGAGATGGGAGTC. LACTATGTTGCCAGGCTGGTCTTGAACTCC. J
GGCTCAAGCGATCCACCCACCTCGGCCACCCAAAGTGCTGGGATTACAGG
CGTAAGCCACCATGCCAGCCCATGTGTGGAAATCTTCTGTTTATCCCTT
TAGGCTTGATTCTTATGTCGTTCTCCTCCCTCCTTCCTGGATACTCCTCT
TGTTCTTTATCTTACTCTACTTGTTCATGTTACCTTGTTTCTGCTTATAAC
TAGCTCCCTCTCCTATCTGAGGAGGGACTTGTGACTGTTCTCATCTCTGT
ACTCCAGCTCCTAGTACATAGCGCTTGCTCAACAGATGTTTGGTGCAAT
GATAGATAAATCACTGGTAGCTGTTACTACCAGTCCTGACTCCCTGCAGT
GCTTCAGCTGATCCTGTTCCAGATGTGCACTGAATATCCTTCTGTTGAAC
AACAGAAATAAAGGGGATGGGTGAGGAGGATAGTCTTCGGTGGCCAAGGA
TATTTTTAGGTACTTTGCAGCACTCAGCAATGAGGAGTGGGCTTTAGTCC
CCCAAGAACTCTCACAGCCCTGGGTGTCTTTACTGTTCAAGTGTCAAATCC
AAGACAAGTCAATGATCAGGAAAGACCATTTTTTTTTTGTTCAGTGAAGTT
TATTTTCAGAATCATTGAACAGTATGATATTTGGTAATTTTATAAATATTC
CCACTTAAATGATCGGAGCAGATATATTTTCAAGTCGTAATTAAAGGACA
TGATTTAAAGAGAGCACACCAGTCCAAATTGAAATGATTCCATAGCTATT
AAAAAACTAGGGTTTTTTTACAGACAATGATACTTTTTTGCCCCCTTTGAAT
AGATTAGACCAATGAATAAAACAAACAAATAAATAAATAAATAGGG
AAGCGGTTGCTCATCAGAATGTGGGAGCGAATGACAGAGGGTTTCTTAGA
ACCAAATGTGGCCGTGGTTTCTGTGAGGCGTGCTTAAAGTGAGTAGGAGA
GGTGAGAGAGGCCTGGCTCAACAAAAGGGCTGGGGATTGTCCCTGAAGAA
CCAGAGCTGANTTNCATCAGGAGTAACANAGGTAGATAG

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CCGCGTTGAGGTTCCACGCAGTTCAAATTATGTCCAATTATCAACATTAA
TGCACATTTTCAATAGAACCTGTTCCGGCTTTTCTTAGGAGGGGGGGCGGG
GAGACGTTGTTCTCTGGGAATAAGTGACGCAGGAGGCTGAGAAGGCTTC
ATTCCATAGCATTCACTTACCTCCAGCTGTAGAGTGGGCTTATCATCTTT
CAACACGCAGGACAGGTACAGATTTTTTTTCTTTGAGGCCCAAGGCCACAG
GTATTTTGTCACTTCTTCTCCTTGTAACAAGGACATGGAGAACACC
ACTGAAGAAAGAAGGGGGTCTTGTGGTTAGGGACACAGCAGTGCAGGGTC
ACCCCAACCCCTAGGCCCATGAGTAGGATACATGTAATTTGGTAGCCTC
TGTGGGAACCCACAGTGAGGTTCTTGGCCTAAGACACAGGATAACTTGA
CTTCTCACAGACAATAGCAGGGTCATTTTGTGATTAGGGTTTCCCCTC
AAAGGCCTGAGGGTTTCTCAGAGCCTCATAGCAGTAGGAACGGAGAATGA
AAGAGGGTCTACATTTTAAATGCTGAAGGAAGGAAGGAAGGAAGCCATTG
TGTCCTGGCTGGCAATGTGCCCATCCACAGGAGCGGAACAACCTTGATCA
ATGTGGAAGGAAGGAAGAGAGGTGAGGCTGTACTTCTGCCAGAAATCAGG
CACCAGAACTGTTTCAGGAACAGAGAGTAGCCCATGGGAAGAACTGGGA
GAGGAGAGGCTGAGCTGGGAAGTGGCTCCAAAGAGAGACACTCATTTTG
ATCTTCTCAGTCACAGCAGTGTCAATTGGAGGCCCTGGGATCACTCTTA
CTACCCGATTCCAAAGAAACAGGATTTTCTTGGCCTGGCTGAGAGCAAAT
AGCTTCCCCCTGAGTGAGGCTGTCCTTCAAAGTCAGCAGCCTTAGTTGCC
CACACTCCTGTGCAGAGGCTTTGGCTACTGTGGCACGATGCCAGGCAGAT
CACCACAGCTAATGATGGGTTCAACGCACCTTGAACTTTTGCCCGTTACA
GCGGAGAGATATAAGTTCCTGCTGGGCGGTAAAATTTCCCTACAAGGAAC
CACCTGGCATTGGGTGGGACGGATGTTGGGGCAAGGGGGGAAGACTGGGG
AGGGGGATGGACACATTATCGCTCCAGCACTCTTGTTTCAGCCTCAACAA
CAGGAAGAGAGAACCCACAGGCAGTTAGGCCATGTCCATCAAATGACCCC
ATATTGTGGAAGAATTGACATTGCACTATGCCCAAGAGACTTGGGTGGAC
ATGGTCCTGGGAGTGCTTGAGCCGTCTAATTTCTCAGGGTCACACTCCTG
TTAACAAATGCACTGGCCAGTGCAATCAAATGTGCCATTTCTAGGACCAA
AGTTTGTATATTCCTTTTAAATATTTTTTTTCACTTGTGTTGATCATTTG
CCTTAAATTAACCTTTCTACTTTGTTTAAACATGGAGAATTAGCAAGCTG
CCAGGAGGCCAGGCAGGGAAACCAGGATGTTTCCATTTACCTTGTTGCTC
CATATCCTGTCCCTGGAGGTGGAGAGCTTTCAGTTCATATGGACCAGACA
TCACCAAGCTTTTTTGCTGTGAGTCCCGGAGCGTGCAAGTTCAGTGATCGT
ACAGGTGCATCGTGACATAAGCTTCGTTATCCCATGTGTGGAAGAAGAT
AGGTTCTGAAATGTGGAGCACATGTTGTTTAGGTATAAATCAGAAGGGC
AGGCCTCGTGAGGCGAGGTGGCAAAATTTGATTTCTTGGAGGACACCTGA
GCATATACGGTCAAAGTCTGATGACAACACCAGTAGGGATGAAGCTGGGA

GTGGGGTGGCTAAGAAC...CTGGACCTGACACTATTAGACATGGGGTTC...
CTTCAGGTCTATTACTGCTCACTGTGGCCGAGCAACAGAGCTACTTAGGT
AAAATGGTGATGGTCATAACACTAGCCCACAGGGAGGTTACGAACCTCTG
GTGACAATGTAAGTGAAAGGCCCTGAGAAAGAGTGAGGGAGTTGCAAAT
GTCAGTAGCCATCAAGATCTTCTTTAAGAATAGTTTCCACTAAAGAGATG
ATTGCTTTGGTTTCCAGCCTTCTTTGTTTTGTCTCCCGCTGGGCCTTCT
ACCTTTAAAGGGCTTTGGCTCTGGGGGAATTGAGTTGGCTGGGGCTTGAT
GACTTCCAAGAGGACACAAGTGGAGATCTACTGCCTGCTCTTGGCTAACT
ACCTTCTTCAAAGATGAAGGGAAAGAAGGTGCTCAGGTCAATTCTCCTGGA
AGGTCTGTGGGCAGGGAACCAGCATCTTCCTCAGCTTGTCCATGGCCACA
ACAACCTGACGCGGCCTGCCTGAAGCCCTTGCTGTAGTGGTGGTCGGAGAT
TCGTAGCTGGATGCCGCCATCCAGAGGGCAGAGGTCCAGGTCTTGGAAAGG
AGCACTGCGGAGAGAGCGAGGGAGGGAGCCTGGTGAGGTGGTCTGCCAG
GAACCATGCTTTGACATCAGAGAGTAGAAAGCTCAGAGAGGAGGAAAGGG
CTTGAAAGAATCCCGAGCTTCTAAAGATCATCCCTCTCTGGGCCAGGCGT
GGTGGCTCATGCCTGTAATCCAGCACTTTGGGAAGCCGAGGTGGATGAA
TCATTTAGGTCAGGACTTCAAAACCAGCCTGGCCAACATGGCGAAACCCC
TTCTCTACTAAAAATACAAAATTAGCTGGGTGTGGTGGGGTGCACCTGT
AATCCTAGCTATTTCAGGAGACTGAGGAAGGAGAATCGCTTGAACCTCAGGA
GGTGGAGGATGCAGTAAGCCAAGATTGTACCACTGCACTCCAGCCTGGGC
AACAGAGTGAGACTCTGTCTCATAAAACAAAACAAAACAAAACAA
AATAAAATAAAATAAAATAAAAGATTATCCCTCTCTGAAGCTCAAGGAG
GTTAAGGGTGTACTCAAGGGCACACAGCAGGTTAGAGGCAGACTCAAGAT
TAGAATGTGGGCTTTCTGACACCTTACAGGCTATTCTTTTAGAATAAATC
CCATTTCTACTTTGTTCATCTTTTTTGTACATGCCCCACCTACACCATAC
ATGTATACCTTCTCTATATCTTTTTTGTATCCCTAATGCTGTCACACTATG
ATTTGCTTTTTTCATGCAGATGACCATAACATTTTCCATTACCTATGCTC
ACTCAGCAAGTATTCAATTTTTCTACACTGTTCTTTTTTTTCTTTTTTCA
TAACACTGTCTCATAGGCATTCTGCAAATCCTGTGAGAGTACTTTTTGTG
AAATGTTACCACTTTCTCTTATTTCAGAGAAGCTCCGTATTAAGGCTTCA
CTGAGGTTGCCTTAAGGCATGATAATGGTTCAAAGGCTTGAAAGACAGTT
AAAGAGACCTGTAAGTGCAAAAAGAAAGTTGAGCAGGAGAGAATTTCTCT
GCCTGGAGCAGAGCCAAGCTGCTGGAAGAGGCAATGGGGGCAAAGGCCAG
GCAGACAAGCCAATGGGCTCCTCCCACAGCTGCAGCCAACAAGTTATGCC
AGTCTTAAAACTTCTAAAGAAATATGTTTTTAACAAGATTGAGGACTGGA
TTATGAGGCTAGGGGAGGCTATCACAACTGGAATAAAATAAAGCCAGAG
AAAAGTGGCTGCCTTCCAACCTGCACAACCTGACCTAGCTAGGCTGATGGC
TGGGCCACCTAGGAAGGCTACTGAGCATCATATAAAACAGAAGGGACAGC
AGGAATATAACATGGCTCTTTGTAAGGATGAGTCTGAAAAATGACCATT
GCTGCCCCAAATGCCCTTAGCTACAACCTGAAAATATTTCAGAACTGGAGGT
TGCAGGATGCTGGAATCTCAGAGATCATCCAGCTCAGCCCTTTATTTTTC
AGATGAGGTCCAAAGCGGGTAAATGACTTGTCAAGGTCAAACAGCAAGT
GAATGGTTTTCTTTCAAGTCTCAATTCATCTTTTGTATTATCATCTAT
GTCTTGTTGTTATAAGCTTCACCCCAGGTAGCAAAAACTATTCTACTCA
AAAGGGGTAGACATATGTTAGTTCTCAAGATCATCTCTTGGTTTCAGAGT
TTAACTCAAGTGATTGGCATAGGCTGAATCCATCTCTTAAAGGATAATC
AAATTTATGTTGAAGACTTGGTTGTCTTCTACTATGAAATGGGAAACAT
TATCACTACTCCTCCCCTGTCACCACCAAGTGTGGCCACCACCACCAACG
TTAGTGAGTGACTGTGGTGATATGATGACCAAGTGGCCAGGTCAGCAAGT
GGTGCAGCCTGTGTCTCACTGGAAGAGGTTAAAGTCTTTCTAAACAAAA
TACCATGGCATCAAAGTGGCCCAGAACTCCCTTCTTTGAGCTTTCCCTGT
GTTAGAGCCCTTCTTGGGTTGGGAGTTAAACCCATAGTCTTACCTTCAT
CTGTTTAGGGCCATCAGCTTCAAAGAACAAGTCATCCTCATTGCCACTGT
AATAAAAACAGGGACATGTCTCAATTATGTCTTCTAAACAGGTTTATTTT
TCCTTCCCTGTGTACAAGACTTGACTGTTTATAAGAACTGCAAACAGCC
TGCCTCTCAAAGCTGCCTGAAACACCTGGCAAGTTTCACAGTGATATGCG
CAGAACAGTCCAGAAGGCAGATTCTAGGCCTGGCAGGTGGGCACCCTGGG
TGCTCCCTGTTGGATCTTGAGGCCTAACCTCTAGCCCAGCAGAGTCAGCT
AAAATCTGAGCTCTCCCTCTCCCTCCAAGCCACACTTTGCAAAGGGATTC
CTTGATTTGTGGGCTTGGAATCTTTTCTCCCCATTGCTCTGCAGGAAG

FIG. 3 (43 of 52)

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CCCTTSCAACACACA TGGATAGCCTCCAGGTCCCAAGGCTGGAGG
CTTGTAATGGGAAAGTAGTCTTTAAATCAGATTTACTTGGCACCTGTTT
GCCACTGAAAGAGGCAATTTAGGGGAAAAATCTGGTCTCCAAGCACAGAT
AACACTCTACTCTTGAAAGAGGAGACCTGCTCATGTTACTGGTCTCAGCG
TCTCCACTGACCTGTAATAAGCCATCATTTCACTGGCGAGCTCAGGTACT
TCTGCCATGGCTGCTTCAGACACCTGTGTAAAAAGGAGAAAAATGAGTGAC
TTCCCCATGACGGCTACGTTTCATGTGTGATTTCTCTCAGCATCCAGTGCA
TGGCAGTCATGCAAAGAAATGATCTCTGAGTAAATGAATGAATGTGTGAA
AGAGAAGTCCCTTGGGTCTAGAGAAAAGCATTGCTAAACCAAACCCCAA
CTAGCAATGTATTGGCTAGGAGAGCTGGAGCAGAGGCTTTGACACTAACC
TTTAGGGTGTCTAGCTGTTAGATAAGCAGTATCCATTCCCAGAATATTTCC
CGAGTCATAAGCATTATATTACACCTGGCATTTTTGCAAAAAGCTGAGAG
AGGGAGGCAGAGAGGGAAGGAGAGGGAGAGACAGAGAAAGAAAGAGAGAG
AGAGAGAGAATATGCATACACACAAAGAGGCAGAGAGACAGAGAGACTCC
CTTAGCACCTAGTTGTAAGGAAGATTAAAGTCATACTTGAGCAATGAAGA
TTGGCTGAAGAGAATCCCAGAGCAGCCTGTTGTGCCTTGTGCCTCGAAGA
GGTTTGGTATCTGCCAGTTTCTCCCTCGCTGTTTTTATAGCTTTCAAAG
CAGAAGTAGGAGGCTGAGAAATTTCTCTGTTGAATACCTGATTTCACAAT
CAAGTTAAAGGAAAGGGGAAAAGAGTATTGGTGGAAGCTTCTTAGGGGAG
GGGACTAATAAACTGAGATAATTCTCTGGTTCATGGAAGGGCAAGGAGTA
GCAAACCTATGACACATTTTGCAAATGTATCACCATGCAAATATGCATTGT
TTTCTGACAATCGTTGTGCAGTTGATGTCCACATTAAATACTGGATTT
TCCCACGTTAGAAGAATGTTTAAATTTAGTATATGTGGGACAAAGTGGAA
GACACACAGATTTATACATGCACATACTTTTCTTCATTCACTTCTTTGTA
CTTAAGTTTAGGAATCTTCCCACCTACAGATGGATAAATGGGTACAATGA
AGGGCCAATAGCCCTCCCTGTCTGTATTGAGGGTGTGGGTCTCTACCTTG
GGTGCTGTTCTCTGCCTCGGGAGCTCTCTGTCAATTGCAGGAGCCTCTGA
GGAGAAAATTGACCTTTCTTGGCTGGGGCAGAGAACATACGGTATGCAGG
GTTCAGGCTCCTGACGGAGTTGGGGCAACCCTGGAGATAAGCTCACACAA
CCCTGCAAGACCAGGTGCTGTTACCCTAGCCAATCTCATGGATGAACCAG
ATCAATGCCAGATGAGCTCTGCCTAAAATGATTTTTTGGTGAACCTCTGAA
AAGTGGAATATTGTTTCTGTAAGAATATCCATCTGAGACTCTATCTCTTG
GTAATACCAAGAGTTATCAGTTTCTCTTTAACCGAGACACCAGCAAAGTG
CCTGCTCCAGGGTAATGCCCAGGGGAGCCCTCCATTTGTAGAATGAATGA
GAGTCCAGGTATGAACAGTGCTGGAGTGTAAGGAACACCCTCCTTTGCC
TCTTTGACAGGTCTGCATCATAACACTTTTTTTTTTTTTTTTGAGACAGAG
TCTCACTCTGTGCGCCAGGCTGGAGTGCAAGTGGCACGATCTCGGCCCCCT
GCAAGTTCCGCCTCCCGGGTTACACCATTTCTCCTGCCTCAGCCTCCCA
GCAGCTGGGACTACAGGCACCTGCCGCCACGCCCGGCTAATTTTTTGAT
TTTTAGTAGAGACAGGGTTTACCATGTAGCCAGGATGGTCTCGATCTC
CTGACCTTGTGATCTGCCCCGCTCGGCCTCCCAAAGTGTTGGGATTACAG
GCGTGAGCCACCGTGTCCAGCCTGTAACACTTCTTATAGCACTGAGTTGA
AACCTTGCTCCTCCTGGTTCTCCAGGAACTGAAATCTTTTTGAGCCAA
GTCTAGCACAGTGCTGGCATGTACATTCAAGGTGGTAGAGTTTGCTGCTT
GAATGGGTGAATGGGAATTTGACAGCATTTTTATTCAAATTAGTATGTGC
CAGGTATCGTGCTCGCTCTGCATTATCCAAGGGAGTGAGCCTCTGTGCAA
GTATTTGAGACACGAGGGAAATAGGTTCTACTGTGGGAAAAAGAGCATTT
CATGGACTTGCTCTCCAAGCAGCCTTCTGATTTTTTAATTTGGCTCCCAGT
ATCTTGATATCAGGAGTCAGTCACAAGAACTCCATCTTTAGTAAGTTATA
TTTTCCACAGGAAATCTAAAAGCTGTTCAACATGTTAGTTTCTGTGAAT
TTGATAAGCCATAATCCATTCCTAACACTGAGCCCTCCTGAAATTTGGTG
TCTGGTCTGTCAGATAGCTAAAAGCCCTGTCTGGGTGGCCTAGGGACTCC
TCTGTTTTGCCTCCACAGGATCCACTTTGCAAATTAACCACTGGTTCTCC
CGTTGTAGGAACTGCCACCTTCTCAGAGCCTGTCTTTCTTCCTTCCTTC
CTTCCTTCCTCTTTCTTTTTCTTTCTCTCTCTCTTTCTTTCTTTCTTTT
CTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCT
TCCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTT
CTCCCTCCCTCCCTCTCTCTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCT
CTTTCTCTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCT
CTCCCTCTCTCTCTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCT
CTCCCTCTCTCTCTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCT

FIG. 3 (44 f 52)

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TCTACCTTTATCCCCCAGCTGGAGTGCAGTGGTACAATCATGCATTCAAT
TGCATGATCACAGCAGCCTCAAACCCTTCCTCAGAGTCTTTATGCGGCAA
CCAGCAGGGTCTGGAGGGTGGTGGCTCTGTGAACCTCTCCTGACAGAACA
CAGAGATGTCTTTGGTCTGTTGATGTGATTACAAGCTGAACGAAGGAAGA
TCAAAGCCAGTGACAGGAAGGGAGATATGCAAGGGACCCGAGCATCAGCT
CTGAGTTAGTCCATTCTGCTTCTGGGACTTGGGATACAGGTGAGAAACCT
TGAGCTTCTACTTCTCCATCTTCCAATTGTAGCATCCAGGACCTCAGAAT
CTGCCAGCTAAGAGGAGCCCTAATGATTGTCTGGTGGGATATGGTGGGAC
CACAGAGATGAAGACATGAATAGCTATTTGAATGTGAACAGCAGACGAAG
AAATCAAGGCTAGGAGGGTGGAAAGTGACTCATCCAATAGCACAGTGTGGT
TGAAGCAGCACTAGTATCCAGGTTGCATGAGCCCCCTGATGCTTTCGCTCG
AGGGAAATTTTGGAGCCATGGGGCAATGCCCCCTGACGTAACAGTCTCCA
CAGTTCTGCCATGTCTCATCCTGGCCCTGTAACCTGGACCCAAATCTGCT
ACCATCCCATCCATCTCAGGAAGTGAAACCTCTTATGTCAAATAGGTTGT
GCAACGTATGTATCAGATCCTGTCTTCCCAAGGAGACCGCTCAGGCCACA
GCACTTCCCTTCCGATCCCCAATGAGCAGAAAATATCTCGCTATAAACATA
GTTGGCACTAAGGGAGGGAGTGGAAGAGTGATGATGATGTAGATGGTGAT
GTAGCCCCAAGGAAGTGGAACAAGCAGAGATGGGGAGCTGGAAATGCCAG
GATGCTCCAGCTTTTGGGGAATTATTCAGCTCTTGAGTCACTAAAGCCTT
TCTCAGCTGCAAGTTCCTCTTTACCCTGTCAGGTCACTTCTTCCAAGACAG
GAGACTGACATTTATTCAAAGCAGCAAGTGCCCTGATACCATCTTGTGTC
TAATCATGGGCTTCGCAGCCAGTTATCAAGGTTGATCTCATCTCATTGGT
CTTCAATCATTTTGAACAAGAAGACAAGCAAAATAATCATGGGTTAGTTC
TTATATTATTGTGTGTACATGCAGTGATGTCTGTTCTTTGTAGTGAGCTG
TTCCTTCCCTTGTTCAACCTCTTGCTTAGAACAGAACTAAGCAATCTGCCC
CCAACATTTTCCCAATTTCCCATCTCATTCTTGGCACTGGCTTCCTAAT
ATTTGTTCTTATGAGTCATTTTCTTGATCATTTCATGAGTCCCTCTGG
GATCTTAAAGTATGAAAAATGTTGTGTGTACCCACACCTGTCTTTGTGGA
TATTTCTCTCCTTTCCCTTCTGCTTCTGGGATTATTTGGGAATGGGCACT
ATGATTTTATCATATCGCTTCCACTTCCCTTATGGCATCATCTCCAATG
GGCTTCTTCTCCCTCTTGGATCCAGGTTCTCAGATTGGGGACATGCAGAG
TCCAAGGAACATTCCATTCTCCTCCCTGGTCTAGAACAAGGAGGGCTTAG
ATATATGAGCAGGTGGCTGGGGCTGGCGAGCTATGTAGTCTCCAATGGCT
TTTCCCTGATGTCGGAGTTGTTATGTGAGTCTGGGAGACCAATAAGACC
TTGTCCTTCCCTTTGGATCCATCAGAAAAAGCCCCTGGGTGGGTAAAGATGG
ATGGCAGGGCTCTCCTACTCTATGTCTTTTCTCACACCTAGTGGGTATAA
GAGAGGGGACCACAAACAGAGGGGGCTCTGGTACCACTTATCCAGGGTCT
GGAAACATTTTCTGTAAAGGGCCAGATAATAATGTTTCAGGTACAATA
CTCAACCTTGCATCATTTCAGAAAAGCAGTCAGATAATACATAAATGAAT
GGGTGTGGCTGGACTTGTCTGCGGTCCCCTGTCTTATATCATTGTATTA
TATCATTTTTTCTTACATACAAATTTAGAAGCAATACTTAAAAA
GCCGTCCTTTATTGAGCACCTACTAAGTGCCAGGTACCTTTTTTCCCTC
ATTATCTTATTAACCTTTCATAATAACCTTTAAAGTAGATAATATTGAAC
CATTTGACCTATGCAGAACTGAGGTTGAGACAATAAATTATTTAAGACC
GCACAAACAGTAAATGCTGGAACCTACGACTCAAATATGGGTAACTGAAC
CAAAACCAGATCTTTATTTCTCACTTTTAATTGTTACATATGTTTATTGC
CTCATCTCCTGTCCACATGGTGCCCATCGGCAGACTCCTTTCTCATTCTC
AGTGATTGAGTGACATTCTAACTACATTGGCCTGGCAGATTCACCTCTG
TCCCCTAAATGTTTCCACATTGTCTTTTAGGATTGAGATCCTCTCTGTT
CCCTTGCTCTTCCCTCCTTTCTTCTTCTGGCGGTGACGTGCTGTGTGAATT
TGTTTCTTTCTCCTCTCAGGGTAGTACTGGGACTTTCCAAATCAGGGTTT
TTAGTGATCTCTCTTCCCTTTTCTGAGTTTCTTCTTATTCCCATTCACT
TTCTCATCTATAAGTGGCAGCTTTGTTGCTGGAGGATTTCTTTGTCTT
TTATTCTTCTTTAAGACTTTGTCTAACTGTCAAAGCAATCCCTTGAAG
GTATCTGTCTTGGAAATTGTGTGCTTATGATGCTGAAAAATACTCTCTTC
CTAAAGCTATTATAAATGCT

>Contig42

GGCTAGCTGCAACTCTTGAATACAAACACATTGAGACATGCACACACTTT
CTGGCTCCCAAAAAGAAAAAATCAATTTATAATAATTCTGATCCT
TTGCTTATTTCCACAACTCCATGAAAATTGTACATTGTCCAAGCAACAT

TTCTTAATATTCTCTT...TCTCTCATATCCATTTTCCTTACTGCTGTC...
CACCTATCTCTTCCAAACTCCCTGTTAAAATCCCTGCCCCAGCGAACTTT
TATTCAATTTTGTGGAATGGAGGCTGCACTGATTTAAATTAAAAA
AAAAAATCCCTACTCCATGTCCCAGATCCCTAGTTGTTTTTTGTTTTTTG
TTTTCTGAGACAGGGTCTTGTGTCTTCCATGCTGGAGTGCAGTGGCATG
ATCATGGCTCACTGCAGCCTCAACCTGCTGGGCTCAAGTAATTCTCTTGC
CTCAGCCTCCCCAGTAGCTGGGAGTTTCAAGGTATGTGCTACCATGCCTAGC
TAATTTTTTTCTTTTATTTTGTAGAGACACGGTCTTGCCAGGTTGCCAG
GCTGGTCTAGAACCCCTGGGCGGACGTGATCCGCCTGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACTGCTCCCGGCCTTGGGTGCAA
TTTGAGCTTTCTCACTTATTAGTGTAAGACATACAGCTAATTTCTAAATC
TTCCAAACCTCAGATTTTTCATCCATGAAGTGAGGATTATTATAGAGCTC
ACTAATAACATGGCTTCAAAAATATATAATGCCAAAATTGAGATCAAAAT
AATAAATCTATATTACATGGGAGATCTTAATGTACCTCTTATATTATTGA
TAGACTAAGATGATCAAAAAAATAGAAAGAGAGCAGTAAGGAGAGCAAGC
ATTTAATCAATAGGACCAATACATTTTAATCAATAGGATCCTCAGGAATA
TATACAGAATACCAAACCTAACAACCTGCAGAAAACATGCCAAACATTTAG
GTACAGACATTGTTGGAAAATGCAATCTTGAAACGAGTGGACTGACATTC
AGAAGATATTAATAAGAGCACTAATGATGGGGATTGCAACCATGTCTTTA
CTGACTTCCAGAAGCTTCTTACAGTAAACATGAAATCACATAATTTCTTC
CACTTTCTCTACTGTTTCTTGTCTGGGCTCTGTCCTGCTTACTGTCTAAT
ATCTTGGCCCCCTTAAAAGTTGCTAATCTTCCAAACCTCATTCTGTGACT
GGGCGCTGGTCTTGTTCATGGGCTTGAAAATACTGACTGTACACTTA
TCTGGAGCATCCAGTGCCTACCACCTGACCCAGATTCTCATTGCGCTCC
TCCCTCCTCCACCTATTGGAATTTGCTCATACCCGTGTGAGACCCCTCCC
TTTCCCCCATCTGAATTTTTATCAAGACAACGCACTGCCATACTCCCTC
GTACCCTGCTCTGGGCATCAGACTGAATGTTTGTTCATTGAGGATCTG
CAGCTGCATCAGTTTCCCCAGCACCGTCCAACCCCTTGAGCATGGCTAGT
CCTAAAGCAGAGAATTAGCCTTTCTATCCCTGCTGCTATACATGCTGGGA
CAAATAATAAGAAATGACAGCATTTTATGATAATGCAGGCTGCAGGAGGC
AGGAGGCAGGAATCAAATTCGTGCTTATCAAATAGTGCTCCAATTCTTTG
AATATTGGACTATAGAATATGTCATGGATCTATGCTCAGGTGGGTTCCTT
ATTACTCACTCCACTGAGGCCAGGTGTGGGATTAGCTGTCCAAGAGGGA
GTTTCAGTCTCACAGCATAGGGTCATTCTGAGAATTACTGGCCACACTT
GTGTGGAGACCTCCAGAGAACAGAATCTGGGTGGTGCCATGTACTTCCA
GGAGGAGAGAAAGTGGCAGGATGCCAGCCCCACAATCAGAGGGGAAGGGG
CAGAGCCACATGTATGAAGATCCTCTCCCCAGTACGTGCCAATCACAGGG
CTTCTAGCTTTTGGGCCAAGGAAACAATGTGGGAAGCAAAAAGGACAA
TTTTCTCTCTCTTTGTCATGAAGACTGAGCAGTTTTTACCAGATTCCCAGG
GAAACACCCCTTCCACTCTGGGTGTAATGTGAGTGAGAGACATTCAGCTGG
AACACTAGAAAACTATTTCTGAGCCACTCACCTTTAGCCCTAGAAAGT
GTTGGATTGTCTCTCATCTTTGCCACAGTAGAGACTGCTGATAGCATCA
GAACTTGGGCTCTGGAATTAGACAGATATGGGTACAAATCTGAGCTCTCT
CACTTATTAGTGTTGGGATGTAGAGCAACTTTTAAAATCCTTCCAAACCTC
AGACTTCTCATGCATGATGTGAGGATTGTAATAGGGCCCACCTAATAGGG
GTTTTTGAGAATTAAAAAGTTATTCAATGAACAGCATTTAGCAAGATGC
CTGACCATTGAGAAAATAACAAATTGTTTATTATTATTGTTATTATTAA
CATCTTTCTGACCTTCTGACTGGGGGCATCGTATCATCAGAAATACTT
AGGATGGGATGGATTCTGTCATGGGCTGAGTCAAGGGTGCAATAATGGAG
GAGTGAAGAAGGAAGAAATGGAGGCAGAAATCCCCAGGAGCCCAGCATGG
TACAAGGCTGAGCTAGTGCTGCAGAGCCTCCTTGGAACAGCCACAGAGCT
TGCATCTGGCCCTGGGAGGAACCTCTTCTAGCTGGCAGGACCAGCCACAA
CAGTGGCCAGGGGATTTCCCAGGGCGTGGGCTCCTAGGAGTTTATTTGGA
CCAAGCCTGCCTGGAGAGGGGTTATAACAGGGATCCTTCCCTACTGGCAG
GTGATTTACCCCTCGGTGAGAAGCTCAGGCATTTGTTTGATGGAAGGTGG
AAGGCCCTGTGCTGGGCCAGTGACTATCAGGGATGGGCGGGTGGCTGGAA
AATAGCAAATAAGACAATATGATAACACAGTTAACCACCACACTATGTGA
AGCTACAATATGGGTATCTGTAATAGACAATTCCAATGTAGAGAATAATT
CTAAGGTGTCATTCTCCCCGCCAATGCCATAAGCACACGGCCTCTGCCTG
GGTTTCTCACTGTGGAATGTCCTCCTGGTCTCCTCATGCCAGAGAGTGG

FIG. 3 (46 of 52)

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GAAGTACTCCTACTTT. .CACCGGCTTTCCTGTCATCTCCCTGCAGCC...
CCTCAGCCCCCTCTGCACAGGGAGGTTTCCCTCCCTGCTGCTGCAGTGCTT
TGTACTTGTAGTGGTACCTGCACACAGGTATTGGTGTCTTGTCTCACC
ACCCTACATCACTGTAAGCTCCCCAGGAGCAGGCTTCCTGTTTGACTCAC
CTGTGATCCTCCACCTCCACCCCTGTAGTGCCTCAAGCATTGAGGACAAT
CACTGGCTGCCCCCTTAACCCAGAAATGCTGCCGAGACAGGAGGCCATGGC
CCAAGTTCCTGGAATGGGGTATTACTATGTCAGCACAAAGGCCCTTGCAC
AAATGAAGGCTTTAAAAATGCAGTCCTAGTCAGGTGGAGGAGGGCTTATA
GGATTTCCAGGAATCTGGATCATTCTCTTGAGAGCTTTCCTTGTCTCTG
TTAAACTCACATCCTACGGCCCAAATAACAACAAAAATGGATGTAAAT
TCTTGAAATAACTTGTGGATGGGGGAACAAGGCCACCCCCCAGATCTGC
CAGAAGCTTCAGGTGAGGGTCCCAAATGCCAAAAAGTCTGGTATCAGAGA
GGATGGCCAGTGACCTGGGGACACATGCCCTTTGCTGTGTCACTCAAGGA
GCAGCAGCCTCGGCCCCGCACAGTGACCAGGACCCTGGCTTCCCACGCTG
GGCAGGAGCTGGTGTCTGATGAAGGGAATGCCTGGCAGCACGTGCTGTCT
GTCTCCTCGTGTCACTTACCTGGCTTTGCTGCGAAGAGGCCACTCGCAT
TTCTCAATTTTTTATATTTTTTTAATTTTTTTAAATTTTTTATTTTATTTT
TATTTTTATTTATTTATTTATTTTAAATTTTTTTTTTAATTTTTTAAATTA
TGCTTTAAGTTTTAGGGTACATGTGCACATTGTGCAGGTAGTTACATAC
GCATACATGCGCCATGCTGGTGCCTGCACCCACTAACTCGTCATCTAGC
ATTAGGTATATCTCCAGTGCTATCCCTCCCCCTCCCCCACCACAA
CAGTCCCCAGAATGTGATGTTCCCTTCCCTGTGTCCATGTGATCTCATTG
AATTTCTTTAAAGGTGGAATCTCTCAGTGGGGTCTAATCTGTTCAGAAAT
ATCAAAAGAGTATCCTTGGGAATGACTGGAATTCCAGAGTCATCTGGTAA
TCCTCATAAAACAACCTCCTGGATGTCTCTCAGCACATCTCCACCTTGAA
CGCAGGAGGCTGGTTCAAATGGAGGAGCATCGCTCTACTGCACTTTTTTT
TTTTTTTGGCCTAAAGTGCAAAAGGGGATACGTTTCATGTAAATAAATCA
ACTGCAAATCGCTAGTTATGCTGAGCCCTGTCCCGTGCTGTGGACACAAA
GGAACCAAAGGCTTTTCTCCCCGCCCAACACACACATAACACACACACAA
AATCATAAAACATACATACCCCCAACACATAACAACACACACACACAC
ACAAAATATATACACACAACACACACCAACATGCCACAAACCTGTGTC
CAGAGATAGATCCTACTGGTGGGTTTGTGGTCTCGCTGACTTCAAGAATG
AAGCCGTGGACCTTCGCAGTGAGTGTTACAGCTCTTAAAGATGGCATGGA
TCCAAAGAGTGAGCAGTAGCAACGTTTACTGTGAAGAGCAAAAGGACAAA
GCTTCCACAACCCAGAAGGGGACCCAGCAGGGTTGCTGGTTGGGGTGGC
CAGCTTTTACTTCCCTTTTGGCCCCCTCCCATGTTCTGTTTCCATCCTATCA
GAGTGCCCTTTTTTCAATCCTCCCTGTGATTGGCTACTTTTAGAATCCTG
CTGATTGGTGCATTTTACAGAGTGCTGATTGGTGCCTTTTACAATCCCCT
TGTAAGACAGAAAAGTTCCTGATTGGTGTGTTTTACAATCCTCTTGTAAG
ACAGAAAAGTTCCTCAAGTCCCCACTGGACCCAGGAAGTCCACGTGGCCT
CACCTTTCAACTCCATAATGGCATGAAAATACATATGTTGTACAAAACAT
ACATACACAAAGTATACATGCATCTCCCCAAATATACACATACCACAGAA
ACATACACACAGGAACTCAGCTACCTGTCAAAAGTCTGCATGGTGTGATTGC
CTCTGCAGTGAGTAGTTAGAAAAGTGAATTTGTTTTTCAATAAATTGGAG
TCCTTAAAAATCGTTGTAAGATAGAAAATTTTTTAAAGTATATAAAATAA
AATATGTATGTCCTTTGGTCTAGCATTTACACATGTAGGAATTTATCCTA
GTGGAGTAATCAATGATATATGCAAAGATTTGGACAAGCATATTAAGCAC
AGAATTATGTATGCATATGTGTGTGTATATATATATATCTCATAcata
TAATAATGTAAAAGTGAAAATAACTCAGATGTTCAAATTTGAGGATTAGT
TAGACTATGATCTGTCCATATGTGACATAACAAGTTAGCTGCCCCCTTATTC
TCTCGAGCTTCAACCTCCTATAAACAGTGTCCCTTGATATCAGTATTGG
TACAGATAATCGAACTTATTGAGGTTTTACATGGGGCAATAAAGGCAAGA
GTTTATGAATACTCCATACTACACTAGGTAGCACCCCCTATTAAAGACAA
ACTCTTCTCTCTCATTTCCCTTCCCTTCCGGAACCACTTGGTTGAATCTC
TACAAGTCTCTATTGCAACTGCCTCAACATGGCACCCCTCCCTGCATCTCC
ATCTTCCCTGTCTGAGAGCAATGGCCTGCTGCCCCCACACTCACATCCT
CATTCAATCCAGAAGTGAGCACCAAGAGTGCTACAGTTACCCCAACC
ACCTTCTTAGAAGATAAGTTAGTGTTTGTGTTTTGACTTTTTTAAATTTTAA
CTTCTCTTTTCTTCACAATCTCATCCCATCCCAAGAGGTTTATCAAGA
AGTTCTCTAAAGATATGTGTCTCCTTATGGAATTTAACAGAAATCAGGGA

FIG. 3 (47 of 52)

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...TTGATTTCTAGCCATC AGGGAATAACATTTTTTCCAGGTCTTTAGAC
ATAATGGAATACCTTGCAGTAATTAGATACACTATTGTAGAAAAGTATTG
ATGAAATGGAACGATGTTTGTAGATATCATATTGAGTAGAAAAGGCAAGAT
ACATTAAGTAGGAAATGTATCTTACAAAATAATTTGTCAGACACACTCCT
ATATTTGTATGTTATATAAATGCGTATGTGAAGAAAGGCTAGAGGATGAG
ACCACAGTCTTCGGTGAAGTTTAAGAGATGATGCTGCAGCATGCTCAGAA
AGGCTTGGTATAGTTTTTTCCAGTAATTAAGGACTGATCTTAGGTAAATT
GTCCATCCTCTCTAAACTGCACCACCTTTTGTCTGTAAAACAGGAAGGAT
GGTATTTACCCCCAGGGTCATCAAAGGATTTGGTTGGAGAAAAATAAATA
AATGGGCTGAGCCCAGACCTGGCACAGTGAGAGCACAGTGGTTGACTATT
GTGCTGGCCTGTTGTTCTGTGTTATTGACATGCTGCTGGTGGTGGTCCA
GAAGCTATTACCTTAATTGGTTATGTGGATTTCCCCCTCATACTGAGCAGC
TGTGTGTGGTGTGTGTA AACATAGCCATACACAGTAACTGACAAGGGCAA
ATGTGATGGAAAAATGCAAGGAAGTGCAGATAAATAGCTAATGGGCTGTA
GAAGGAAGCTAGTCCTTGGAGGGCTTGATCAAGGAAGGTCCTTTTGCATG
TCACCTTTGAAGAAGAGGGGACATAGAAGAGGTATAGTGCATCCCGGAGT
GTACCTGGAAGGGAACATGAAAAGAGGACATTTTTCTCTGGGACATGGGG
ACTCCACTTGCATGAACTCTGGAATTGGGGCAAAGAACCATCATGAGAAC
AAGGGCTTCCTTGAACCTCCCAGGCTCATTGGCTGATCTAAACCCTGTGT
CCCCCTCTTTCCTTCACTCTCCTCTGTTTTCTATACCTGTATTATTGGACT
GGACTGGAAGCCACCTGATCTATCACAAGTACCTTGAAATGTGTTGAATA
GGTGTGGCACAGTCCTTAGCAGAGTGGCACTACCCCCACAGGAATTTGTT
TATACCTTTGGCATGGAAAAATAGCAGGAAATGAGTGATCACTGATAACTG
AGGATGCTATTTATTATTGGCCAAAGGAATACTTGTGTTGTATTTGCATA
ACCACTCACAACTGTTGATTACAAATGAGTACCAGACCTAGCTCCTTCA
AGTAAAGGATCTTGAGAACTGAAGGCAAACAGAGCTCCAGGAGTCCAAGA
CAGAGCCACAGACCACGAGGATCCCTGGCCCCAGGTAGGTGGTCCTCCTGC
ACTGGCTTTCAAGGCCAACAGGATGGATGGGGAAGTAGAGTAGCATCTGG
CCATCTAGACCCTTGCTTTTTTATCCCCACTGGAAGCACATCTGAATTTCT
AAATATGATCTCTGAGACCTGCCCAGAACACCTTGCTCTCAGCCCCAGTA
GCAGCCTGCTCTCTCCCAGGAGGGCTTCCACTAACAAGTAGGGCATTGCT
GGAGGGCCAGGCAGACACTAGCTTAGGAAATCCACCAACCCTGGAAATGC
TAGTCCCTTCTCTGAAGGCTCAGAAGACTGACTTTAGAGTCTAGAAAATA
TTGGTCCTTGGGAACAGATTTTGTAGTGCAAAGAGATGGACTTCAGATGGC
CAGATGCACTGCTTCTTTAGGGAATTCTGTGAAAGCTCCCTGCATTTATC
TTAATACAGGCAGCAGATTTTATGAGTACCCCCGAGGGATGGCCCCAGGT
CCTCCAGCCTGTGAGCATCCTTCTGTCTTTCAGCAGCACCACAGTATCTT
TATATGTCTTTGGATACCTACGTTTCTGCCAGACATCTCTTGCTCTGATG
TTCTGGCTGCCAAATTCTCTGTCAAGCGCCTCCAATTTTTTGTGTCCTTT
GATTTACCCCCAACATGACAAAGGCAGTTGTGCTTCATGTATTTCAGGGATA
CTGCCAAACCACAAACAGGTTAAAATCAAATAGCAGATATCCCTGTTCTT
AAAGACCCATCAGCTCTACCCACCTGCTCCTGCTCACCGTCCTTATTGTT
GAGTCCTGAAGCCCTTCTTGTCAATTTTTTATTTTTTGCATGAACAATTTA
GTTCCCTTTGTCTCACTCCTAAACCTTTCTCAAAGGATTGGATTTGTACA
CAAACCTGCCTATCTCTGCAATCTTAGAAGTGATATGATTCTGAACAAATC
ACTTAACTTTTGATTTTTTATTGGTAAGATGGGAATACCAATTTTTTGCTC
CACTTCTGTCTTATGTTGGCCTGGGCTGATGTTGAAAGCTCTCGGTCAAC
TGAGATAGGGTGTGCAGAAATTTATATATATAAATATATCTCCTCCAACCC
CTCCCAATGAAGCAAGTCACGTGAGTCAATCCTACCCTAAGATATTAGGG
ATTGAGCCTCCTGGGACATTTGGTGGCTTAGGTTTTTCATGAAAAGAGGTT
GCAGAGCAACTGCTTTTTTGTAGGCAAAGATTAGGCTACTGCAGAGACTC
AGCAAACCTTCTATAGAAGGTGTCAGATGGTAAGTATTTTAGGCTTTGCTT
GCCAGATGATCTCTCAACTAGTTAACCATGCTATTGTAGCCTCGAAGCAG
CCAGAGACGATCTGTAAACAAGAGCATGTAGTGTGGCATAAATATAGTA
CCGCG
>Contig43
GCAATAAGTCTATTTACTGTAAAGTTAATCAAATTTACATTTTCAGAACAC
TTAATCTGCAAGAGTCCTTTCCAAGACCCTATACCTAATTTTGTGTTTAC
AATTTTATATTTGTTTTCTTAAAGAAGACCACCAATATAAACTATATCCA
GCCTTCATGATAAGTACATAAGAACTATGCAAATAAGGGGGAAAAAAA

FIG. 3 (48 of 52)

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CAAAGAAAAATACCTAC .TTACTAATGGTTCACCTTCTGAATAGGACAT...
TCATAATGATACAAGCACTCATTACTAGTCTAGGAAAATGAAGATATAAT
TGCATTAGGAAGATCAAGAGGTAGGAAATGTGGATGTGTGTGGTATAGAC
TAGGGCAGGACAAAGAACCTAAATCCTCATTTTCTAAAGATAATTGTTAA
TACGTAAAACTCAAAATTCAAGAAGTAACAGTAAAAGCGGTCATTAAGAA
ACAAGCACTAAACACCAGATAGGAAGCGAGAGATGGGGGAAGAGGGCAAG
AATCTGATTATTTTTTTGCAACAAATTTTGTAAAACCATTTGACTGTTTAC
ATGTAGAACTTGGATCTTTTTTTAAAAAACACAAAATAATAACTATTAT
TTTTTAACTGGATTTTTTGAAAAAGAAGATAAAAGTCTCATTTTAGTAATT
AAAACCTCATTCCAGGTTAGTCCACTCAAACTTATATTCGAAAATTAAAA
CTTTGGGAGGCTGAGGCAGGCAGATCACCTGAGGTTGGGAGTTCGAGACC
AGCCTGACCAACACGGAGAAACCCCGTCTCTACTAAAAATACAAAATTAG
CTGGGCGTTGTGCATGCCTGTAATCCCAGCTACTCGGGAGGCTGAGGCAG
GAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGATCACA
CCATTGCACTCCAGCCTGGGCAACAAGAGTGAACTCCATCTCAAAAAAA
AAAAAAAAAAAAAATTAAACCTCTGGAAGTTGAGTTTGCAGATATTCAT
TATGCTCATTTTTTAACTTGTATGTTTGGAAAATGTCATGATGAGAATTGA
GGTTGGGGGATGAGAAAAAAGAAAAACATCAACCCACAGCCCATTCAA
TTTTCAGCCCGACCCACAGCTCCGGGGAAGGGCAGCAGGTCCATCCTTCA
CTCTTTCTTCACCTCTTTCCCTCCTTCTGGCTCTTCCACCTCTAAGTTG
GAGCCCAAGAAGAGGCACTGGGAAATGGAAAAGTCTTTTGTACGTGGTAC
TTGCCGGGGAAGCTGCCATGAAGACCTGGCCCCACGGTGGGGAGGGGAATG
CCCAGCTGAGGCCTCGTGCCCATGCTAGGATAGACTCGTCCAGACATGTC
AGGTGGTCTGACAGGGCAAGCAGCAGGAAGTCATGTATGAGTATGAACTG
ATCTGTATGCAAGGGCGGGGAGAACACGCGGAGGAATGGGGCGTGAGAAA
ACAGCACAGTACGTTTCTTTAGCAGCTGTCTCTGCTCAGCCATGGGAGTC
ACCAGAGAAAGAGGCTTGGAGGCGTTATTTTCACTGTGAGATGTGAGTGT
AAAAAAGTGCCCAAGACACAGTGAGTACCAGGGAGATGCCCTCTTTCCCT
ACCCGAATGCAGAATGGCCACAGGCCTTAAACACACACATGGTTCCTCA
GAGGAGAGAGGCCTCCACAGTGGAACCCGCATTCTCCCCTGGTCAGCAG
CAGCAGGGCGAGTGCTGGGCCATCATGAAGCTTCACAGGCAATGAGCTCT
CAGCAATAACAGGAACAGTGCTGGGGGACTGTAGCTGCAAGACCGATTT
TCATGTAAGATGGCCTCTGAGGACTCCGAGATACACCAGGCTGAGACTAG
CTGGCAGCTCCAAGTTCTTGGTCAGAAGAGAACAGGAAGTAGGGAAATTG
GAATTACTGTTACTACAATTCTTTTACATCCGCACAACCATGAGGTCCAG
AGAGTCTCTCTTATTTTTTTTTTTTAAAGACAGGGTCTCACTCTGTCGCCCCA
GCCTAGAGTGCACCTGGTGTGATCATGGTTCAGTACAGTCTTCACCTCCCA
GGCTCAAGTGACCCTCCTGCCTCAGCCTCTCAAGTGGCTGGGACAGCAGT
TGCATGCTACCAGGCCTGGCTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT
TCGGTAGAGACTGGGTCTCTCTGTATTGCCCAGGCTAGTCTCGAACTCCT
GGGCTCAAGTGATCCTCTGGCCTCAGCCTCCCAAAGTGTTGGAATTACAG
GCATGAGACACTGCACCCAGCCAGTATAGTCTTTTAAACAGCTTTATTGAG
GTACGGCTAACATTGAAAAAACTACACAAATGTAAAGTATGCAATTTGAT
AATTTTGACAAATGTACACACCAGTGAACTATCACTACAGTCAAAATAA
TGAACATATCCATCACTCCCAATTTCTCAGCCCCCTTGGTAACCCCTCT
CTCCCAACTCCCTGCCCCCTAACATCAGACAACCTACTGATGCATTCTGTC
TCCATAGGCTCATTTACATTTTCTAGAATTTTACATAAATAAAATGACAG
AGTATATACTCCTTCATGTATGGCTTCTTTCAGCCCAATTATGTCAAGAT
TCATGCTTATGGCTGTGCGTATCCTTAGCCCATCTCTTTGTCTTGCTGAG
TAGGATACCATTGCATAGACAGACCACAGCTTGCTCATCCATTCACCTCTT
GACAACGTTGAATTGTCTCTGTTTTTTGCAATGACAAATAAGGTTGCTAT
GTACATTCTGTATAGACATTTGTAAAAGCACAGCATTTTCTTTCTCTTG
GGTAAAGACCTAAAAGTGGAAGGCTGAGTCATATGGTAAATATATATGT
CTAACTTTTTAAGAACTGTCAAAGTGTACCCAAAGGGATTGTACAATT
TTACATCCCCACCAGCAGTGATGAAAATTCCCGTACTTCCACATCCTCA
CCAATATATGGTGTGGTCAATCTTTTTTAATTTTGGACATGNTAATGAGTG
CAAAATGAGGCCAGAGTGTCTGAAGTTACATTTGTATCCTTTTTTGGCAT
CCAAAACAGGTGTCAAGCATAGAAAAAACACTTGTTCCTTGAATGGTCAG
TCATTTACAAGTGGAATTCATTACAAACCGGTAGTTCTACTGGGTAAAC
TATGCCTTACTGTCAACAGGCACATACACATACAGACAGACAGGAAGGCA

FIG. 3 (49 of 52)

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CAGAGACAAGGCAGAGC...TGATAAGAAGGTGACCTGGGCTCTAGCTCT...
GCCTATCACCTAGTAAAATATTAGTTAAGTAGCCATGAGTAACTCACTTA
ACTTACCACAGGCTCCATTTTCTTATCTGTAAAATAGGAACATTGAAACA
GCTAATCCCCAAGGTTTGTGGATAATCAGAATTACAAAGATCAATGACAT
TTCTATGAGAGAAACATATTTCCAAGTATTTGATGGAGTACATCAGACAC
AAAGGAAAGGAACTGAATATTTTTTGAGGTTTTTTTTTTTACCAAGAAA
TTCACATTTTGTAAATTTTCAGAACTACCTCCTGAGGAAAGTGTAGCTG
CACTTCATTTAGAATGATAGAAAACATCAATCTGTCTGATTCCAAAGCCAA
GTTCTTGCTACAACGAGAAATGAAACAACCTGGATCCCTACAGATGCAGAG
ACCTGGGCCCCACAAATGTGAATTCTGTTCCCTACCGAATAGAGTTACA
GTTCCATAATACAGTACTCCCTCACTTTTCCACAGTCTCACATTCCACAG
TTTCAGTTACCCACAGTCAACTGCAATCCAAAAATATTAATGAAAAATTC
CAAAAATAAACAATTTCAGAAGTTTTAAATTGTGCTCCATTCTGAGTAGCG
TGATAAAATCTTGTGCCACCATCCACCTGTCCAGCTTATCGTTAGTCAT
TGACATCGTCTGCTCCTGACATCCAACCATTGACATCATCATGACTCTAT
GATCCAGGATCACCGAAGCAGATGACCCTCCTTCTGACATATCATCAGGC
CAATATCAGCCTAAACACTGCATCACTATGCCACATCAGTCACCTCACT
TCATCTCATCAAGGAGGCAATGGATCACCTCACATCATCACAAGAAGAAG
AGTGGGTATAGAACAATAAGATAATTTTGGGGCAGGCATGGTGGCTCACG
CTTGTAATCCCAATACTTTGGGAGGCCAAGGCAGGAGGATCCCTTGGGCC
CAGGCATTCAAAACCAGCCTGGGAAACATAGTGAGACCTCCTCTCTCTGC
AAAAAAAATAAACAATAATTATCCAGATACAGTGGTGCATGCCTGTGGTC
CCAGCTACTCAGGAGGCTAAAGTGGGAGGATCACTTGGTCCCAGGAGGTC
GAGGCAGCAGTAAGCTGTGATCGTGCCACTGCACTCCAGCCTGGGCAATA
AAGTGAGACCCTGTCTCAAAAAAAAAAGGTAATTTTGAGAAAGAGACCAC
ATTCATACAACCTTTTATTATAGTATATTGTTAGAATTGTTCTATTTTCATT
ACTTATTGTTGTTAATTTCTTTCTTTGCCTAATTTTTTTTTTTTTTTTG
AGTCGGAGTTTCACTCTTGTGTTGCCAGGCTGTAGTGCAATGAGACGATCT
CAGCTCACCGCAAATCCCGCCTCCCGGGTTCAAGTGATTCTCCTGCCTCA
GCCTCCCGAGTAGCTGGGATTACAGGCGCCTGCCACCATGCCCAGCTAAT
TTTGTATTTTGTAGTAGAGGCGGGGTTTCTCCATGTTGGTCAGGCTGGTCT
CGAACTCCTGACCTCAGGTGAGGCCTCAGCCTCCTAAAGTGCTGGGATTA
CAGGCTTGAGCCACTGCGCCTGGCCTCTTTGCCTAATTTATAAATTAAC
ATTGTCACAGGCATGTATTAATTTATAGGAAATCATAGACATATAGAGT
TGGGTACTATCCACAGTTTCAGGCATTCACTGAGGGGCTTGGAACACGCC
CTCCTCAGATGAGGGGGGACTACTGTCTCTCCTCAATCATTCTTGATTCT
AATCCTCAACACAAATGGTTTGGCCAGGTCTTGCCTCTGGAGACAAAATT
GCTAAGGATTTAGAGGGGAAAAAATGTAGTTCACTGGGAAAGTCACCTCT
GCTCCACTGGACAGCAACTTAAACCCAGGCCATGACAAGTAGAAAGGCC
ACCCCCACTCTCCTTCACACCTGGAGTATTCAGGAGTCAATCATATTTCA
GGACCACCAGGAGCAAACTGGGAAAACTGAGCTGCCTTGAGGAAAGCAA
TCAGCTCCACAAGGGGCTTAAGAAACAAGCTCTGGGAGGAGTGGTTGGAG
AAGAGTTGGGGACACATCAGAAATGCCATCAAATTTCTAAGGGCTACCTC
GTGGTGTGACACCTGTGCATCTTCAAGGACATAAACAGATGGGATAAGCA
GATGAGATTCACAGAGGACATCAAAATATTGGCTCCCCAGAAGGGAGAAC
ATTCTAGTAACAGAGCTGCCCAGCTGCAGAGTGGACTGTTTCACAAAGCA
ACAGGTGCCCTGCCTCTTGAATCACCATCTTCACAGGAATGCAGTAGAAG
GGACTTAACTCCTGCCCTGAAGAAAAGGTTAGGCTAGGGAAACAGCTCCA
AAATTTTTTAAAGGAAGCAACATAGGCATCTACTGGGAGTTTTCTAAAG
CCTTTGTTTAAATGAACTAAAGAGCTGGGACAGGAAATGCCAAATTAAT
TAATAGAGCCTTGCTTTAAGACAATGCAAGTGGATGGTAATGAAGGAATG
AGTCTTAGGCCTTGGATCAACCGTATTAAGCAATGCTGAGCATGGAGCCA
ATTCTGTTCACTAGATTTGCTCAGAAAGGGCCAGACGAGAAGGATTTTTC
TAAAGGCACCTACTACCAAAAAGCTGCCAAGGCGTCCAATGGAGCCCAGA
GAGAATATGCTAACAATAAAAAGTTGAACACCCTCAATAAAAAAGGGTAA
AAGTAATTAATAGAAAATTACTGAAAGCTTTTTTGAACCAAAAGTAGTC
AGCATTGGTAAAAGTCTACAAAAGTGGACACTTTCATATAATGTTGGCAG
GAGGGTAAAAGACATAACCTTTTTGGAGGACAATTTGGCAACAGAGTAC
CAAAAACCTTACAATTGAAGAGAACTTTGGCCTGAGTGCAGTGGCTCACA
CCTGTAATGCCAACACTTTGGAAGGCCAAGGTGGGAGGATTGCTTGAGCC

FIG. 3 (50 of 52)

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CAAAAGTTTGAGACCAGCCTGGGGTAACACAGTAAGACCTCGTCTCTATG
AAAAATAAGAAAAGTTAGCTGGGCATGGTGGCATGTGCCTGTGGTCCCAA
CTACTTGAGAGACTGAGGCAGGAGGATCGCTTGAGCCTCGGAGGTCAAGG
CTGCTGTGAGCCATGTTTCATGCGACTGTTCTCCAGTCTGGGTGACAGAAT
GAGACCTGTCTCACCAGAAAAACAAGGCAAGAGAGAGAGAGAGAGAGAA
GGAGAGAAAGAAAAGAAAAGAAAAGAAAAGAAAAGATGGAAGGAAGGAAA
GAGAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAA
AAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGAAAAGGAGAGAAAAGGA
AGGAAGGAAAAGAAAAGCAAGCAAGCAGGAAAAGGAAGGAAGGAAGGA
GGAAGGAAGGAAGAAAAGAAAAGAAAAGAAAAGGAGAGGGAAAAGGAAA
GAAAAGGACAAAAGAAAAGACCTTTGAACCTGAATTTCACTTTTAGAGA
TTCATCTTAAGGAAATTCATTCCAATAGAAATTTATCCCCAGGATTATCT
AAATATTTGCTTTTATTTTCTTCTAGTAATTTTATGGTTTAACTTTCTCA
TGTTTAAAGCCTTTAATTTATTTTGAATTTATTTTGGTATGAGAAAGTGTG
ACCTTTTTTTTGTTTTACTTTAAAAAAATGTATTACGATTATTTTATTTAG
AGACAGGGTCTTGCTCTGTCACCCAGGCTAGAGTGCAGTGGTGTGATCAT
AGCTCACTGCAGCCTTGAACCTCTGGCCTCAAGCAATTCTCCCTCTTCAA
CTTAGGAGTAGCTGGGACCACAGGCATGTACCACCATGCCCACTAATTT
TTTTTATTTTTTTGTAGAGACAGAGTCTTGCTTGTTGCCCAGTCTTGCAAT
GTTGTCTCAAACCTCTGGGCTCAAGTGATCCTGTGCGCCCCAGCCTECCAA
AGCACTGGGATTACACGTGTGAGCCACTGCGCCCAGCTGCCTTTTTATTT
TTTAATTTTTCAGATGCTTTGTTGGTTCCAAAATAGCACTTATTAACCCA
CGCTTTCCCCCTCTGGTTTTAAATACTGCAAGTTTGGCTTTGAAATACAA
CCCCTGCTTATTTCAGGCTACATTCAAGGAAATCTGAGACCAAGAGTCT
GAAGGCCAGTTTCTTCTCAAAACCCAGGAGGTGGTAAATGTGTCACTT
CCACACTTTCTATCTATTTCTAAGAACTCCTTCTTTCCAAACTCTGACAT
GCCCCTGGCTCAGGTCTATAGAAATTCCCAGGGTCCACAGACAAAGCAGA
ACTCACTTATGGGGAAATCTGGGAAATACTTATCTGTAAACCTGCCCCA
TATGGTGAATCAGATTGTCTAAAGCCCAAAGCATCATTTTCCACCCCAA
CCATTTCTCTCTCCAGACTTCTCTATTTCTGTGGTCCAGAGTCAAGATCT
TGATATTACCTAGAGTCCCCCTTCTGCTCTCCTGCATACCCAGATGCCC
CTCCCTCCCCAGATCCATTCTCCACCCCTCCCTCCCATCAGTTTGGTGGG
CCCATCACCGCTTCCCCTGGCCCAGGCTCTCCTTTTGTGCGCTTGGAGCA
GCAGACTGATCTCCAGCCTTCACTCACTTCATGTGGTAATCTGTTGTGT
TCATCACTGTGAGAATCTTCTGCATCCCCTCACTACTCTGCTGAAAACAC
TCTAGTGGTTCCTCATTGCTCATTAAATGAAAGTCTAGATATTAAACGTAG
AAGGCCCAGCACAAATTTGCCCCATGCCACCTACCTCTCTAATCTTTTCT
CCTTACTCTGACAGACTCTCCGTCTGTCAATTTATGTATTCTTTTATTGCT
CTCTTCTACTTTTAGTATGAACTGGATTTATGGATTTTTTTTAAACATTGCT
TTCAAGTATGGAATAAAGAATTTTATTTATTTATTTATTTATTTGA
GACTGGGTCTCACTCTGTTGCCCAGGCCAGAATGCAATGGTGCAGTCATA
TCTCACTGTAACCTCGAATTCCTAGGCTCAAGCCATCCTCCTGCCTCAGC
CTCCTAAGTAGCTATGACTACGGGTGTGCATCACCACATCTGGCTAATGG
AATAAAATATTACAATGCCTAATCTTAATTTTCAAATTTTAAATTACAT
TGTAACCTAATGCCCATGCATTTACTTTTTTCAAGTGGGTCAATAGCCCTCA
CTTTGGCAAAGGTCCCAGGCCCAAGGTAAGGCCTTACTTTTTCCAAACTC
ATCTTTTGAAAGACATAAGTGCCTGTAAGTTGTACCACATTAGGTTCTAG
GAATTTTTTCATCAAAGACTTTATCAGACTATTTTCTCTAAGTTGAGAAA
GAGCTGGGGGCAGAATATGGCACTGAATGACTGAAGAGAAGGCACTGAAA
TCAGGCCAGAGGTTGCTGGAAAGAGCAATGAGGAACACCAGCAGCAATGA
GGAGCCGGTGATGATTTTGGCTTCACAGGGAGGTGTGTACCACACCGATT
TTATCTCTACGTGGATGAACCACAGCTGTCGGCTCCCTTGTCTCCAGGAC
ATCACACTCTCCACATTCCTTCCCATCTTCCGGCTTCTGCTTCCCGGGGC
CCTCATCTGCCCCATCCTGGGTGAACACTGGTCCGTCAACTGCTGGGCGT
ACCTTCCCGCTCTGCACACCCTCCCTGGCCACCCCACTCTCACGGC
TCGCACTGCAGAGGAGCCGCATCTCTAGCTCCAGCCCATCTGCCTCTTCT
GAGCTCTAACTTCATGTAGGCGACTCCTGCCGGTGTGCTTCCAGGCCC
ATCATACTTCAAAGCATTTTCCCCTCAGAACACCATGTCCTGGCTGCTCC
CTCCAGAAGATACATCTCTCAAGCACATCCCCGCGGCTCTCACCTGGATG

FIG. 3 (51 of 52)

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ACTGCATTACCTTCTC ACATTTGCCCTCCTTTGGATGTATATAGA.
GTTTTAAAATACAAATCTGATGTGCTTGCTCTCCTGCTTGAAACACCTCA
AAACTGCCTTCAGGATAAACCACTGCCCTTGACATGTTTACAGGTTGCCC
ATGGCCTGGCCCTGCCCATCTCTTCAGCCTCATCTCATGCCCTTGCCCC
TCGCTCTCTGGGCTTCTGCCTCCCTAGCCCTCCTTTAGGTTCTCTAACAC
ACCATAGTCCTTCTAGTGTTGGGGCCTCTGCAAGTGCTGTTCCCATTGCC
TGAGACATGAATCCCTCTCCCTATCTCTACCTGCACCTTCATCTGATTAA
TCCCTACCCTTCCTACTCATGATGTTGCTTTCTCAGGGACTCTCTCTGAC
TTTTTAAACTAATCAGGGTCTCCCCAGTATATATCTTCATAGCACTCTGT
ATTACTCCTTTCTTAATGACCACCTGCTGTAGACTGAATGTTTGTCTTCC
TCCAAAATTCATATGTTAAACCTAGCCCCAAATGTGATAATATTTGGAG
GAAGGCTCTTTGGGAGGCAGAGCCCTCATGAATGGGATTAGTAGCCTTAT
AAAAGAGACCCCTGAGGGCTCCCTTGTCCCTCCACCGTGTAAGGATGCA
ACAAGAAAGTATGGTCTATGATCCAAAAGCAGACCCTTGCCAGGTACCC
AATATGCTGGCACTTGAACCTCCAGCCTCCAGAACTGTGAGAAATAAAT
TTCTATTTTTTCATAAGCCACCGAGTCTATGGTATTTTGTATAGGAGCAC
AAACAGACTGATGTGCCACCCAACCATGATTATACGTGTAATTTATGGTT
TCTCTGCTAGTAGGGATGCACCATGGGGTTAGGAACCACGCTTTTCTTAT
TTCCACACAGTCCTTAGCTCTAAGCATGTTCTCTGAATCAAAGATCCCCA
TCTTTTATGAATGAAGGAGTCAGTGAATGAATTAATGAAAGAACTGATAA
CCCTCAATAATTATTCAGCCTTTTATACCTACTATTAACAAGCTTGCAT
TCTACTCCAAATTTATTGGGCTTTAACTCTATTTTTTGGCCAGCCACATTT
GACATTCCCTGAAGTAAATCTATGCTTTCCATCCTAAGTCAAGGAAGGAC
CTGGACTAGTAGGGCCAAGAAAGGTCTAAATTCATGGGTGGGAGAGAGA
GACTAAATCTGAAAGGAAGAATAGATTGAGCAAAGGTGTAGAGATTGGGG
AAGGCTGGACATTTGGAGAGAAGGAAAGGAAACTGACACTAAACCAAC
AGTCTCACAAACACAATCTCATCCTTCCAAAACCTCTGTGAAGTAAGAATT
ACTATCCCAGGGCCAGGCACAGTGGCCCATGCCTGTAATCCCAGCACTTT
GGGAGGCCAAGGTGGGTGGATCACCTGAAGTCAGGAGTTCAAGACCAACC
TGATCAACATGGTGAAACCCCATCTCTACTAAAAATACAAAATTAGCTGG
GCATGGTGGTGACACCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGG
AGAATCATTTGAACCTGGGAGGTGGAGGTTGCAGTGAGCAGAGATCGTGC
CACTGCACTCCAGCCTGGGTGACAGGGAGACTCCGTCTCAAAAAAAAAAA
AACAAAAAAAAAAACCAAAAAAAAAAACAAAAACAAGAATTACTATCCCAG
TTTTGCAGATGAGGCAATGGAAGCTCTAAAAAGTTAAGTAGGAGAAACAA
ACATGAAATGTATGTCTTATGCTTTTCTCATCCTATTTCTCAGCCTGG
AATGTCCATTCTCCCTCCACTATGCAAATCTAACTCTTCAAGCTAACACA
TAGCAATGTCTGAGAAACCGTCCCTGTGTTCACTCTGTTAGCCTCACTTG
CTCCCTCCCATCCCTCTGTTTCTTTCTGTTATAACACTTCTCTATTCT
GCTGGCATCACAGTCATCTCCACCTGCCTTCCTCACAAGTTAAAAGCTTG
TTAAGGGCAAGTGGTGTCTTTGCCACCTCATTCCCCAGGGCTTCTAACA
CAGTGCCTCATGCATGACAGAGTTGTAAAACAGGTTACCAAGCTGGCTTC
AGGCAGGTTTGCATGGAACCTGTGCTTTACAGGAATACCTGCTCCCCCAG
GCCCTGGGTCTTCCTCCTGAGTCCAGGCTCAGACTCTCTCATCCTGCTCG
TTCTCTCTTGGGGAGCCACAGTAACTTTGAGCAACTTTGCATGGGATAGA
ATGGCCTATTAGGGGCAGCACAAAGACCCCATGGAGGGAAGAGTACAGAA
AGGGAAAACGATAATCATATTTTTTTAAGATGTGCATTTTCTTAACAAA
TGCTCTAGTACTTGTCCAGACTTTCAAACCTCAAAAACCTAAGCGTCCTTT
TCTTGAAGATCATCAAAGGCCCCAGTGGTCTTCAGGTATGTCAAGCTTT
CTAGAAAATAAAGGTAAGTCATAATCACTTAACACACATGGCTAAATGGC
CATTTCTTCTAATTTATCAGCAACTGTTACATATTTCTATACTAGAAA
AATTTATATTTATACTCAGGGTGGTAAGTTAAATTTGCCATCGAAGTAAA
GCAGAAAGAGCGTAGCATGTATGTATATGTAACCTCAACTGTGCATGAGAC
AAAGATGTCTTGAGGAGAATGAGTCTAAGATGCGCCTGAGCAATAGTACC
C

FIG. 3 (52 of 52)

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GCACCCATGTTTCTAAAGGGCATAACCAGCCATAATAACAGGATGGGTGAG
GATATAGACAGCAGATGACAGAGAGGAGAGTGAAAGCTGGGAATCCCAGC
TAAAGGCATCAGGTTTATGGAATGAGTAGGGGACAATACTGTGTGTGTTT
ATACACACATGTATATGTGTGTATATGTATACATGTTTATGTATATATAT
AATTATATGGTACCATTTCTAATTGACAAAATAATCTATCACATTTTACA
TTATCAGATTTTACATCTATTGTTCTAAATACACTCAGTCATCAGCCCTG
TGTGTGGGCTCTTACCCATCCCCATGCACACCTCAGCTCAACCACTGATG
GATGGATCATCTGCCTATCAGAGGTGGCATATTTCAGGTGAATCCATGGCC
ACAGCTGCAGCACTTCCTACCCACGCAGAAAGGCTCCACAAGAGGAGGCA
CACCCGCTCTGACTGTCCCTAAGCTCCTGACATCTTCACCCCATGAAACT
GCTGCTCCTGGGTGCTTCCTGCCTTGCCCTGCCACCCCTTGTACTGTTCT
CACCATTGACACAGCTGGTGCCCGATGCAC

>Contig2

NAAAACGAATCGTCACTATTGAAGCCTGTCTCTCANC GGATCGTGACTAA
GAACCCCTCCTTGCTTCAAGTTGTCTGCTTTCTAGGCAGAGCCACCC
TACATCTTAAATATATTGATTGATGACTTACGTCTCCCTAAAATATATAA
AACCAAGCTGTGCTCTTACCAACTTGGGCACATGTGGTCAAGACCTCCTG
ATGCTCTTGTCATGAGTGGGTGGGTGTTCTCAACCTTGAAAAATAAACT
TTCTAAATTAAGTGAACCTGGGTGAGATTTTGGGGTTCACAGCAACAA
TTTAAAAAACTCACCATTGACCTGAAATTTTGACCTTATGCTGTCTCTCA
CACTCCTCCATGAAAATAGACGCCATCCTATGAGTTCCCTCAGCCATGTC
ATGCCACACTTCCAACATGTGTCCCATCCACCATCTGTCTTCTTATTGC
TGCATCCTACCCAGGCCCTGATCTCTGGACCCATTGTTGTATAATTAAGA
ATTTGGGGCTGGGCATCGTGGCTGTGGCTCACTCCTGTGATCTCAACATT
TTGGGAAGGTGTATTAGTCAGGATTCTCTCCGAAGGATGCAACCCTAGGGA
TCCTCTCTATGACCCTATGTCTA

>Contig3

CGCGCTCAACCGACCGATTTGCGCGAACCTGCCCATGCCCGAGGACAGTG
TAATCCTAAACGTCCCCTGAATCATAAGGATATGAGTGCGAAAGTACGG
TTCCCTCTGTCACTACTTTCTAACAACGCTATGTCCGATCCGTGCACTAA
CCCCGCCAAGTCACTGAAACACTGATGGGCGCTTCCTCTACAGGTATCC
AGGGCCAATACCACTACTCCCCTCCTCCCTGTCCCCCTTCCACTCTCTAG
AGGCCGCGGATGCCATCCTCTATTAGCACAACCGAAAACGACGGTGAAAG
TACCACGAAGCTCACGATCTGATCGGTGCCCCAATGCGGTTACAACGGCT
GTCATCCCAACCCCCGTCCCATCCTCCATATTGCCCCCCCCCTATGAGGAT
GGCCCTATCATCATGACCTCCAAAATTCTGTCTCTCCCGACGTAATGCC
GCCCTCTGAACGCCTGACACCATCAAGTCNGTCACCTCCCAAATACTCC
TCCTAATCACCAGGCCGAGTATCCCCGGTTCCACAATACCTCCTTGAGAC
GGGCCGATATCACACAC

>Contig4

NGGAGTTTAGGTCAACTAGTAACAAGTGGGATTTGCGACTCAGGTCTATC
TAATCCTCAAACCCACGTCTTGACCCCTACACAGACTGCCCTCCCTCAG
TCCTCTGTGTGGCCTCAAGAAGGGTCTGGACATTCAAGTTTAAAAATCCA
TCCAAAGAATCTATGGACCCAGTGGTCTCTGGAGTCAATGTTCTGAGGCT
CAGAAGGGCCAGGCAGGAGGGAGCCGCTCTACACAGTCTTGAGCAGAGT
GGGCTGTGTCCCGGCACAGCAGGGGAGATCATAAACAGAATTCTGCCCTG
GGCCCTATTTAAGTAGGACCTTTAGGCTGCCGGTGTGATGACCACAGGTC
CCANGTCTGCACGATTGGCTGTGTGTGGAAAATCTTCACTCCTTGCGGCC
TTGTCTCTTGGCAGAGAGCACCGCTGCTTCTCTGATGGCCACCAGGGGA
GGCGCTCCCCTGGGAACGGTTTGAANGGGAGCCTCACCCACACGTGCCT
TCCGTGGTACCCAGCACAGCTGCTACCCATGGTTACCCACAGGCCAGC
TCTGCTCTGAAGAAGGAGGAGTGGTGGCGATCANGCCTTGTCTGCATCCC
GTGGCTGCCCTTTCTTTTCTTT

>Contig5

GGGAGCTAACCGCTCACTGGGATTACAGGTACGCACCACCACGCCTGGCT
AATTTTGTATTTTATAGTAGAGACGGGGTTTCTCCGTGTTGGTAAGGCTGG
TCTCGAACTCCCAACCTCAGTTGATCTGCCCGCCTCAGCCTCCCAAAGTG
CTGGGATAACAGGTGTGAGCTACCATGCCTGGGCTTATATGTTTCTAGTC
CAAACATTTAGCTACCTTTTTTTTTTTTTTTTGAGACGAAGTCTCACTCTGT

FIG. 4 (1 f 61)

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TGCCCCAAGCTGGAGCACAGTGGCACAATCGTGGCTCGCTGCAGCCTCAAC
CTCCTCAGGCTCAGGTGATTCTCCACCTCGGCCTCCCTAGTAGCTGGGA
CTACAGGTACGCACCACTACACCCTGCTAATTTTTTTGTTTTTGTATTTT
TTGTACAGATGGGGTTTCTTCATGTTACCCANGCTGGTCTTGAACCTCTG
GGCTCAAGCAATCTGCCTACTTCAGCCTCCCAAAGTGCTAGGATTACAAG
CATAAGCCACCATAACCCGGCCTACCTACTTTTAACTTGTGGAATTTTCTA
TAAGGTCANGGATGCCTGNGGGAACAAAAGTTTCTCCCTTGGTATATGCA
AGTAAAATCCACATGCTGCCTCCC

>Contig6

AGGACTGTAGCTGTTGTCTAGTCACCAGGCTGGACTGCTTGGCATGATCT
CAGCTCACTACAACCTCCACCTCCTGGGTTCAAGGGATTCTCCTGCTTCA
GCCTTCCAAGTAGCTGGGATTACAGGCATGCACTACCATGCCCGGCTAAT
TTTGTATTCTTAGTAGAGACGGGGTTTCGCCATGTTGGCCAGGCTGCTCT
CAAACCTCCTGCCCTCAAGTGATCTGCCTGCCTCGGCCTCCCAAAGTGCTG
GGATTACAGGCGTGAGCCCCCGGCCACATGTAAAAGTTTATATCTCTGT
TGTTTCACCTTGTTTTTGACCTAGTCTTTCAGTGATTTGAATCTTGATT
AGTCTTTTGTATTATTTAGTGGTACTTCCCAGCTTTGTGTCTATCTGTGGAT
GACATATGAGTCTTGCTTCTTCATGCCAATTTAAGAAGACTGAACGGGAA
TAGGTCAAAGGCATGGCCATGAGCGATTTCTCTCCAGCTTTTCATGGTGT
TCAGCTTCAAATCTATTACATATTGGACCTGCAAGCCATCATCTTATCC
ACAGGCTATCATCATAGGTGAATGTAAATTGGGTTTAGGTGGCCAAGCTG
AACGTGAGATATNTTC

>Contig7

AGCATGTTCTCTAAAGGCCTATCAAAGCTGACATCAAAGGGATAAGTTCC
AGTTACCCAGCTGAAGGGAAGGAGGGTGTTTCAGATAGAGGAAGGATAAG
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GAACCTGAAATTGTGTCAAAGAGCTTGGATGCAAAGAGCCGTGGGAGACT
ATTGGGGGTTTTAAGCAGGGATATAATATTCAATCAAGCATGCAGTAAA
GGTCACTGGCACCTGCCATGGGCCAGGACTCGGGCTCTACATGATTGCGT
CTGTTTTTGAAATATCACCTGGCTGTGAGATGAAGAACAGGTAGGAGGG
TCACAAAACCTTGAAGCAGAGAGACTGTTGAGGAAGTAAGCTGTTTTTGTG
TGGACTGTGGCAATCACAGAGGCAGAGGATATAAATGCACAGAGACACAA
GGCATGTGGGAGGCAGAAGGAATCAAATACAATGAGTGATCAGATGTGGG
GTTAGAATGGTGAGTGANAAGACATACTCAAGGTGACACGCCAGGTAT
CTGGGTGGATGGTAAGACATTCATGGACTAGAATCGAAGAGGAGGTGGGG
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ATGGAGAGGATTAACCAGGAATCCGGTGCCTTTTTTCCAAACTGGGTTGGA
GGGG

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GGTGAATGCTTTGGCACGCTGTGTAGATTTTAGGTGACGGGTGGTGACAA
TGAGTCCGTGTCGAGCGCTGATTTTTTTCGGCCTTTAGAGCGAGATTTATA
CAATAGAATTTGGCATGAGATTGGATTGCTTTTAGTCAGCCTCTTATAGC
CTAAAGTCTTTGAGTGACTAGATGACATATCATGTAAGTTGCTGATAGGT
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GAAAACGGGAACGCTTTCTCATAAAGAGTAACAGAACGACCGTGTAAGTGC
GAATGAAGCTCGCCATAACATAAGTCGTTTTTGTCTCCCGAATATCAGACC
AGTCAACAAGTGTCATGGGCTCGTATTGCCCGAACAGATTAAGCTAGCA
TGCCAACGGGATAAACGAGTCGCTCTTGGTGGAGGG

>Contig9

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CTCACAAGACTAGGGGAAGGATAAAGGCAGGTGAGTCACTCTAGGATGGC
TCANTGAGCTCCACAGAGCTGGAACACAGGCACCAGGAGGGATTCAGAG
CAGGCCTCAGTGCACGTCAGCTGAGTGAACCAATGAGCAGGTGATGGGTC
CAGGCAGAGCCCTGTCCTCTTTAGGCAAAAACCTTGAAACACCGTTCCC
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AGCCCCAAGGAAGTGGTATGGTGAACAGAAAGGGCCATTTCCTGTCCAATG
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GAAATCCTTTCTCTTTTCGAGAAACCAACCAAAACCGCGAAATTCA
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CTGTGTTTAAATTAATTCTACCCTGGTTCTCGGCCCTTACTGCGAAGGTG
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>Contig10

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CGTTGATCCATCTCTGTACGCACTTGTCAACATGGCAGGAGTACGGGAGC
TGCGAGAATCCTCTCTGTGATGTCCCACGGAGCATGCCGTGAGACAACG
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GGATACTCACTCGTGCATGCGGCAATAGATCGATACGCAGTCGTACGCC
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CGCACTCGAGATCTGAACGCACGTCTTAACCTGCCAGTACTCGTGAGACC
TATACTGCGCAAGCCTTGGCTAGGAGATCCTGCAGCGCCGGCAAAGAATC
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ATTAACCTCTGAATGTGCTGCAAGCAGACGGTTGCTCAACATATATATGG
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CACGTCTGAGTGTACGCACGTTACTC

>Contig11

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TTATGCTGTAATGGCACCGCTCACCCTGGGCTTATGAGCAGACCTAACCC
TCCCANAGTGCTGGGATTACAGGCATGAGCCACCGTGCCCGGCCAGTAT
CTGAACTTCTGTGGCCAGGCAGAAAAGGTCCTGTGTTACTCGTCTCCTTT
ATCATTTCATGTCCATATTCTCCCATTTGCTAACATTTATGTTTCTGCTCC
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GGTCTTTGAATATTTGGTCCACTTTTCCTGCAAAGTCCCCTCTCACCTTA
TCTTCCTGGTAAACTTCCAGCCAACACCTCTTTACTAACCAGAGAAACAT
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CATTGTCAATGTGGCAGAGATGCACCTTAGATACCTCTTTGAGAAAGGAC
TCACTGCCCAGCTGCCTGGCACGTGATGAGCTGATAGCTCCAGCTATAGA
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GGTGGCCTCCCCAGTGATGACTAAGGCAGTGTTACAATGGCCTAGTCATT
TCCTCCCAATGCTGGACTCCCAATGAACCATCTGCTCCGGAGCTTCCCAC
TGGGCAGTCAGAGACCTTAGCTAGTCTGCCTCCGAATCAGAAGGCTCTCT
CTTGCCACTCTGGCC

>Contig12

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TGTGTCCTCTTAATGGCAGTCATTCACCATCTTCCTGTCCCTCCCCTTCA
TTTCTTGGATGGTGAAGTGTCACTTTGCTGCAACAGAACCTGTCCCAATC
CTTGATGGTTCAATACACACATAGACATTCTTTTTAACAGGGCGGCCTCT
CAGGTCTTTAATTTTCTTCCCTCCAATAACCTTGTGATGATCCCCAGCT
TAGCCACTTACTGCCAGATCATTACCAGTAACTCCAGCCCCCTCCTTAATT
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>Contig13

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>Contig14

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TCAC

>Contig15

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TCAATCCAATAGTGTGTGTCTCCCTGTGAACTCACGGATATACCGATTTT
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GAATCATGGATGACTATGTTGAAGTCCATCTATAAAGTTCAACCCCATC
TCCGTCCCTGATTCCCCCTCCCCAAGATCACCAACGCGACTCGACATATT
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>Contig16

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GCTGTTTCCTG

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>Contig18

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>Contig19

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TGTCCCCTCCACCGTGTAAGGATGCAACAAGAAAGTATGGTCTATGATCC
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CATGATTATACGTGTAATTTATGGTTTCTCTGCTAGTAGGGATGCACCAT
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TATACCTACTATTAA

>Contig20

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TATCTGTTAGAACAGAAGACACGAAAATATAATAACAATATTCATTTATC
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GTCTTAATCTAACGCTATAGTAGGCATATTATGTTTCGTATTATCCTGATT
GAATGTGTGATGTGAACCTGACTTTAAGTAATCAGGATTGAATTCCATTAG
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GC

>Contig21

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CATATATATATATGACCCATAAAAAGGAGATAAATCAACACTTCAGAACT
GACCCAACTTGCAAAGATACTATAATTAACAGAAAAGGACAGTTTACTA
AGTACTCCGTATGTTCAACAAGTGAAAGATTAAACATATTAAGTAGAGAT
GTAGAAGATATAAGAAGATCCAAAATGAACTTTTAGAGTTGAAAACCTACA
ATATTTAAGATAAAAAATACACTAGGTGGGATTAAAAGTAGATTACACATT
GCATAAGATAAAAAAAATGAGCCTGAATACAGCACAGTATAAACTATCT
TAAACAAAAACACAGAGAGAAAAAATAACTTTAGAGACTTAGCTCTTATC
CTCTATTTGTTTCTAAACAGAGGATAAGGGGCAGAAAAAATGTTTGAAGA
AATCATGATTTTTTAAATTTCCAACCTGAGATAGGAATAGCACTGGGTAGTC
ACAGGAGGCTGGAAAGACCCAAACAGCAGTTAAACAGGAACTAGGCAAA
GAAACCAAAGGATAACAGTAAACCTAACTAAGGGAGAGAAAACCTGACAA
AAGCTGACTTAGGATAACTGAC

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CCTTTTATAACCTCTATAACCTTTATTAAGGAGTAGGTTAATGCTTCAAG
AAAACCTTGTTAATCTGACACAGGACCCATATGCTGATCTTGCATCAGTG
TGGCTTGGACATCAATGATTATGATTAATTTATAGAGAAATTGAACTTAT
TTTATCTCTCAAATTTGGCCCTTACAATCTCACACACCCACCTCTTCCAC
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TGCTTGGACTTTCTGGTTTGTCGTGAACATCCTTTTCTTTCTTTCTTTCT
TTTTTAAATTTTACTTTACGTTCTGGGATACATGTGAAGAACATGGAGGT
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CGTCATCTATATTAGGTATTTTTCTTAATGTTATCCCTCCCCTTGCCCCC
CACCTCCTGACAGGCCCTGGTGTGGGACATCCCCTCCCTGTGTCCATGTG
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CTGTTC

>Contig23

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TCCCTAAGCAATACAATATAACAACCTATTTATATAGCATTACGCTGTAT
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CCTCAGATTTTGGTATCCATGGCAGTCTTGAGTCAATTCTCCTGCAACA
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CATATGGTTTTTTTACTATTTATTAATGTAATGAATTAGACCAATTTTCTA
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CTAGGGCTTTTACAAAAGGAGACTCTAGAATGCCATTTTCGGTTTCCTTG
ATGTGTATTGGCCTCTTTCATTTAGGCTTTTGGATTTTTTAGGGCATT
TTCATATAGGCTTTTACC

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CATAAACTTCAGGTTGGATGTTTCGGTCAAAGTGGTCCGGCGATGCGAAAA
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TCGTGACAGAGAGAGGGACAGTGACAGCGCACACAGTGCAGGGTCCATG
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TCCTGTACTGACCACCCAGGATTTGGGTAGACTGTACGAGTTAATGAGCA
TGGTCCCCAACAAGACTGCTTCGACCTCAGATGCAAAGCACACTTCAGGG
GTCCCCAAGCCACTCATGTTTTTTGAATGACTGCCATAAGTTCAAAAATT
CCCACAATTCTCTCAGATTCAATAACTGGGTATAACCACTCATAGAACTC
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GCACATCAAGTGCTCATCAACCAGGAAGTTCCTCTGAGCTCCAATGTCCA
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GTGATCATTTCACTCACCTTGTTTATGATGAGAGGTGCCACCATCTGGCC
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CTCAAGCATCAATGTTTTTTAAAGCTCCAATTTTAAGGATCATTACATTA
TGTCGAAGAAATTATAGTATTTACGCCTTACTGACTGTAAACCACCACCA
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FIG. 4 (7 of 61)

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CCAGGTACTCAAATCAATTCATTGCATCCCAAATCCCAGATGGGCCACC
CTTATTGACAAATTCAGCCCAATCTTGGTTGAACACATTTAGAATATATT
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TGGCCCAGTAATGGCATTTCAGAAATCCACCAAATATTAAGATGCTTTT
TGAAAAATATCCAGAGCACTCATGTAAAAGTGCTTAATTATTAATAAAAG
CTGACATGTGTTGGGTACTTCTGTGGGTCTGGCACTAGGCTAATTATGT
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GAATGATACTCAAATTAGTAACCAGAGCCCATGCTCTTAAACACTATGCT
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CGCATTAACAACCTTAGGAATCAGACAAAATATACAAAGCATTGTTTGT
ACACATTGGATAACAGACAGCACTAGATAGTCGTGTCTGAGAAAAGCGGT
GAAATGAGCTGAGTCTTAGAATTGCCCCAGTTTACTAAGGGGCATAGTAA
GGGCATAGCTGCAGCACAAAGAAGCAGAACCCAAACAGAGACTGGCGTTCA
CCTGAGTTGAGAAAACCAAGTTGAAAATTTAGGAACACTAACACAGATAT
GTAGGCAAGAGTATCAGAGAGGAGACAGTTGTAGGGAAAAAGAGAGCTTT
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TCATTTATGTTTCCACCAGCCAGAGTGGAACAACCTTGTAACGCATATGG
AGTACTCAAACGAATATTTCTCAATAATAAGTTCAAATTAAGTGAAGT
AAAGCCTGCCCCGCTTTGTCTGGACATGCCTAACAAAGCTTTGAGGGAAGC
CTCAAAGAATGAAACCGTGTCCAAGTAATTTAACTGTGTCCAGAAAAA
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AGGCCTAGAAAGTATACATATGATAAAATTAGCAGACATTAAATGGTTAT
GATTAATTTATTTTATATGTTAAAGAAGGTAGAGAAGAGCATAAGCACAT
TAAAGAGAGACAGGAAAGTCCCAGTACTCACACAGGGCCAGGAGCAGTTT
TCACCAGTCAGGTGGGAAAACCTTCATATTTTCATGGAGCATTGGTAGAGTA
CACAGTGTCTTGCCTTAGTAGAGGGATAAATGCTGTTCTGTTCCCGCCTA
ACCCATCTTGAAAGAAAATCTGAAAGGATCAAACCTGTATTCAAGTAACCT
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ATATCTAGAAACACAAAATAATATCTAGCACCCAACAAGGTAAAATTCA
CAATGTCTAGCATTCAATTGAAATTTTCTAGGCCATCAAAGAAGCAGTAA
AATATGACCTATAAGGCCGGGCACATTGGCTCATGCCTGTAATCCCAGCA
CTCTGGGAGGCCAAGGTGGGTGGCTCACCCGGAGGTCAGGAGTTCAAGAC
CAGCCTGGTCAACATGGTGAGACCTCATCTCTACTAAAAATATAAAAATT
AGCCCAGCATGGTGGTGGGCGCCTGTAATCCCAGCTACTCAGGAGGTTGA
GGCAGGAGAATCGCTTGAACCTGGGAGAAGGAGACCGCAGTGAGCCAAGA
TGGCACCAATGCACTGCAGCCTCATTAGAGAACATCGGGAAG

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TGTGAGAGAAGGAGACTGACAGTCTGTGGGTGTGTATGCAGTGTGGGGG
AAGCGAGGCACAGGGGACAATACTGTGGTGTAGAAAACCTAGTCTAAGGTA
GCATCAGGAAATTCATGAAACCAAAATGAATTTTCATAACAGCACAAAGACA
TTATTTGTTTTTGCCTCCCTCTCATTTTTTTTTTTTTTTTGAACAGAGTC
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AACCTCCACCTCCAGGGTTCAAGCAATTCTCATGCCTCAGCCTCCTGAGT
AGCTGATTACAGGTCTGCACCACCCCGCCGGCTAGTTTTTGTATTTTTAG
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TACTAGTGTCCAGTGGAGTTTTTTAGGGGCTACATAACATGATACTGTCA
TTAATCTAATGGCTAATGAAAGGGATATGTATATGTTTTTGTGTTTAAAA
CAAACCTTCTTTGGGGTCCTCAATAATTTTTTAAGAGTATAAAGGGGTCCTG
AGATCAAAGAGTTTGAGTTCGTGCTGGACTGGGACAGTGGTTGTCAACCCA
GATTGTACATTAGGGTCATCTGGGAAGCTTTAAATAGTACTGATGCCCA
ACCTTACCGCAAACCAATTAAGCCAGAATCTCTGTGGATGAGAAGTCTTC
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ATCATCATCATATCATCTTCATTATCATTGTTAGTATCTCCATCACC
ATCATCAGCATCACCATTATTATCATCATCATCATCCCCACCATCATCCT
CATCGGAACTTCACCTGCATGGAGGACAATCCACTATGCATTAGGTGCTA
TGCTATTTGCTATACTCCTTATTCTCACAACCTGCCCAGAGAGGCTGATAT
TATCTCACTTTATAACAGGAGGAATCTGGATCGGAAAAGTTAAGGTAAGC
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TGCATGTGTCTTTATAGCAGCATGATTTATAATCCTTTGGGTATATACCC
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GAATTGCCACACTGTCTACCACAATGGTTGAATTAGTTTATAGCCCCACC
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TTATAGATTTTATAAGCAAATTGTATTTACTGTGCAAGAATTGGTTTATT
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CCCTATAAACGAGCCAATATGAAGAGAAGGCCTTAATGTGGTTAACTATG
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ATCTCCTAATTCTACCTTGGTGGATTTTAGACTGACCACAACTCATGGGT
AAATGAGGGAAGACGAATAAGAAACCTTGCTTTTTTTTCTCCTTGTTTT
TGGCTGGCTGCAGTGGCTCACACCTGTAATCTCATCACTTTGGGAGGCCA
AGGTGGGAAGATCACTTGAGCTCAGGATTTCAAACTGGCCTGGGCAACA
TAGTGAGACCCCATCTCTAAAAAAGGCGACGG
GCGGTGCGTGCCTGTAATCCTACCTACTCAAAAAGCCGAGGTGGAAAGAT
CACTTGAGCATGGGAGGTCAAAGCTGCAGTGAACCTTGATTGCACCACTT
CATTCCAGCCTGGGTGACAAAGCAGGACGCTGCCTCAAAAAACAAAAAC
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CTGGCTTTGTGTATGCCAGAGAATGGGGGCAGGAAAGAGAGATTGGTGTC
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AACCTTCCAGATACAGAGACACAACCTTCCCCAAGAGGTCCTCATTTGCTC
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TTTGAGGTCNCAAGATTTATTTTCTTTTCAAAAGGTGATCACTACCATA
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CTATAACAACCTGTATCAGTACT

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AAGTGGACCGTGTGGCCAGAAGAGTCCCGCACTGCACTCTAGTGACAGTG
CAGAAAGTCACTGTGGGAAATCTAGAAGTTTCTACAGGTTGCTATTTTCAT
CATAGCACTGTGCAGGCCAACCTTCTGCTCCACTGGCTGTTGGGAAAA
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ACCTCCACACAGTAGATTGCCTCAAGGCCCAATTCCAATATGAATAAAAA
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CCTGCCCCCACCAGTAAAGACTTAGCTGGGAAAGTCAGCTTCATGTGAG
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CAGGCCTGAGCTTCTGTCATGTGGGAGGAAAGAGAAAGAGAGAAACT
CCAAGATCCAAGAGATCCAGCAAGAAGGCTGGAGTCTGAGGACGCAGAAA
GCTGAATGGCACAGTTACCACTATTGTGCTGAGGTTCTGTGGCCTCTGGG
TCTCTTGACAACCTGGGCAAAGACCCACAGAAAATCTCTAGACCCTAC

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GGATCGAGGAGAGCTTGTTAGGCAGAGAAAATACCCAAGGGCAAGGGAGA
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TGCCAGGTGGACTGGAGATGGGGCTGAGGAGCTGTCACAGAGCATTCTG
GACACAGATGTCACATAGTCCCTTGAGGTTAGGGTCCTTAGGCATGGCAG
CATTGCTTTGAGTTTTTCTTTTGTAATGTTGCCATTTCATGACAATGTGG
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TAAGATGTGAGCCAAGGAAAATGAGGAACACCTGAACACTGGGGCAGGTG
CAGGGCCCAGAGAGAAGCAGATGGCTTCTGAGGTTTTAAGTAGGTAGAA
TCAAGGCAGCTGGTAAAGATCTTTTATTACATATAAACTGGAATAAGCCA
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CAGAGTTGAGAGATGGGACCTTTAAAAGGTGATTAGGTCATAAGGGTTCT
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CCTTTCCACCTTCTGCTATGGGATGACACAGCAAGAAGGCCCTCACCAGA
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AAATTTCTGTTTATTATAAATTACCCAGTCTCAGGTATTCTGTTCTAGAA
GCACAAAATGGACTAAGATCATTAGATTATCATTTTTTATCAGACTGTTG
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GCTCATGCCTATAATCCCAGCACTTTGGGAGGCCAAGGCAGGTGGATTGC
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TCTACTAAAATACAAAAAACTAGGCCGGGCGCGGTGGCTCACGTCTGTAA
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GAGCCGAGATTGCGCCACTGCAGTCCGCAGTCCCGCCTGGGCGACAGAGC
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GTGCCTATAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATTGCTTGA
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GCCATCTCTCATAGGATTTGCAGACCAAATCCAAATACTTAAAATAGCAA
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GTAATCCCANCACTTTGGGAGGCCAGGCGGGTGGATCACTTGAGGTCAG
TAGTTTGAGACCAGTCTGGCCGACATGGCGAAACCCCGTCTCTACTAAA
ATACAAAATTAGCCCGGCATGGTGGCACATGCCTGTAATCCCAACTACT

FIG. 4 (22 f 61)

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TGGGAGGCTGAGGCACGAJAATTGCTTGAACCTCGAGAGGCGGAGGTTGCA
GTGAGCCGAGACTGCGGCCATTGCCCTCCAGCCTGGGCGATGAGAGCGAA
ACTTCATCGAAAAACAAAAACAAAAACAAAAACACCTTAGAAGA
AGCGTTCCTCCTCTTGCTTTCTGAAGACACTCTACGCTGAAACAGTAACT
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TTTGTGTGCAAGATCCAATAAGCCTCTCTTGCGGTCTGGATGAGAACCCT
TTTTTTGAATACTCTGACACAACAAATTGCAGAAAGAAAGTCTCACATG
TATAAAATAAGCAAAAAGATTCTCTGGCATCTGAAGAAACAATTCCTTG
TCAATATTAGTATCACTATAAGTGTAGAACAACCTGTTGTATGATGCTAC
ATAAAGTATATGAATCTGAATACTGTTGGATACAAAGGGAGACTATNNAA
TGTAATACGTGCCCCGAAATGACTACACTGTTGGTGATCTTTCTTTCAAG
AAGCANAATATTGCCTCNAACATCCTGTACATGGTATAAAATTTTA

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CCCAGCAAGAACACCAATACAACGGGGGGGGCGTTCTTTGTGAGGGGTGG
GGAGGTCAATTTTTTTGGAACCTGCAGCAGGTAACACACAAAACCTTCCACA
GCTGCTACCAGCTTTCCAGGAGAGCCTGTGTACCTGGAGAGGAGAAGGCA
AGTGCTTCCGAACCTGACTTGATGTCTTAGATTCTGCAATGCGTAGTCTG
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GGTCTGGAAGACAGACTTGGTGGGTGGGTGGCTGCTACAACACCCCTAGTT
AGAGGTAGAGGGGTAAGTCAGTGTGTCTTCTGCACAGGCCTCTTCCCCAC
CTCATTCTTCATTTCCCATACAGCCTTGCTGAGTTATTCACAAACATCTG
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CCTCATTTCTCCTCTGTATAATGTGGGGGTGGGGGAAAGTTCTGGTCA
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CAAGCAAGAGAACAGGATGGAGAATAACCGGATGGGTGCAATCGGAGGTG
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CAGGTGGCTGAATGTACAGAAGCTGCCAATCATGAAAGATCTGGGGTACA
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GGCTTAGCACAAATGTGGCATGGCAAGAAGGCCAGTGTGGCTGAAGCAGC
ATGAACAATGGGTGGAGGGGCTGAGAGGACAGAGGAGCAGGAAAGAGCCA
GGCTTGGGTAGGAGAGGTGTCACTTGATATATGATGCAAAGCCCTTGGA
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GCCTCCCAAGTAACTGGGATTACAGGCGCCACCAACAGGCCAGCTAAT
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TTAACACTTAAATGAGGTCAAATTGATCACCTTTTTATTTATGGTTGATT
CCTTTGGTGTCTGTGTAAAGGAATGTTGTTCTTCTTCTGTCCTTCTGCTG
AAAGATTTCTTGTGTATTTTGTCTTAAAGTTTTAAAGTTTTGCTTTTCC
CATCTGTGCACATTTACATTTGCTACATCTCACTGACTGCTTCTCTGCTG
TGCAGAGCAAGCTCCATGAGAGCAGGAGGCATGGGTCTGCTTCTTGTG
GTCCCCAGAGCCCTATGTCTGACTAGGACCTGGCAGGGGACTAGTGAGT
AGCTCCTGACTAACTGACTCAATGAATGAATGATTGGATGATTGAACAAA
GTGGTATGGGAGTTCACAGCGAGTAAGAGATGCCTTAGAAGAGATGAAGA
AGGAGATGGTATAGGGTAGTGGTCTCAATTCTGGGTCCATGGTGGACTC
ACCTGGGGACCCTTAAATGTACCGTGGAGGATCCAGCCCAAGAGATTC
TGTATGACTGGTCTAAGATGTGGTCTGGGCACCAGGTGATCCCAGTGTGC
AGCCAGGCCTGAGGCCACTGGATTTGGTGGTAAATGAGGTAACATCAAG
GGTACAGACGTTGGTTGCCAACAGGCTTGGGCTTGAATTTAAGCTTTGTC
ACTGACTTGCTGTCTCTCTGCACTCGTTGAGCCTGTTTTCTCAGCTGA
GAGATGGGTGTGATAACACCTACCTGCTGTAGTTGTTGTGAGAGTTAGAG
GAGATAAGCATGTTCTTGAATGAAGTGTGTTCTTAATCCATCATAGGTT
TTTTGCTTGTGTTGTTGTTGTTGTTGTTGTTTTCTTTTCAAGAATGA
GGTTGAGCCAGACTTTGACAGCTGGGTGGGAAGTGAACATGTGGTGATTG
GGAGAGAAGGGCAGTTTATGTGAAGGGAATGTAATAATTAGAGAGTGGGC
GTGGGAAGACATGCTGGGGAGAGTGAGCAGGCCGTTAGCCCTGGTAGAG
GGTGCAAGAGAGCAGTGCGGAATCTGCCAGGGAGACAGGTGGGTGACCAG
GGTGCCAAGGGTGTGGCTTTTCCCAGGTTCCTATGGACACAGCCATCCTC
CCAGATGCCCAGCCTAGCTGTGAGTGAGCAAGAGTTCTGGATTGTCTCTC
TCACTCTGTCTTTTCTCTCATTCCAGAAACAAAGCAGTGACTGGTACTT
AGGAGGAGAATCAGGTCAAGTTGGGAGAACTTGCTTCTGCTCAGGGGAG
CAGAAGCAAGAATGGAGGCCCCACCCATGCTGGAAGATGATGAGGGTTTT
GGTTCAGGGAGGAGGAATATTGGGGATCTAAAGGGGCCTGGGAGTGGGGC
AGGACCCTGCCTTAGGACAGGTAGAAACATTTTCTATAAAAAATGGGGTG
GAGGTTGATGGTAGGACCAGGCATCTTTAGTTGGCTCCCTGGAGTGTCAA
GCCCTTGAGATGGTCTTTAAAGCCATGCAGTGGGGTTTGAATCTGGTGT
TCAAGCTCATAGGTTATTAACATAATGACACTTGGAACATTTTGGGAGA
GCTCAAGTGAGTGGCCTGGAAGTTCTGTGTTGGTGCAGGAGGTGACTTAG
GATGTGCTGCTCCAGACTCATATCTTTGACTGCACACCTGATGCTTCATC
TGGCTATCCTGTAAGCACCTTCAACTTAACATGTCTACACAGAACTCTT
GATATTCCTGTTCTTCCCCAGTTCCTCAGTTCTTACCAAATGTTCTTCC
AGTTACCCAATTGCTCAAGTAAAAAATCTAAGTCCTTCTCTTGGATTTCT
GCCTGTTCCCTCAACATCCCACCTATCCATGAGTGTCTGTGGGCCCTGC
CTCTGAAATAAATCCTGCCTTTGTCTCCCAGTTCACTCCAGCCACCCATC
CTGGGGCTGCACCCTCCTCCTTCCAAGCCCTCTCCCTTTCTTCTGCTG
CTGCCTGTCTGTCAGCATATGCATCAGTGCGACCAGGACATTTGAAAT
GCAACCAGTACAATTGGGCGCGGTTATGCCTACCAGTTTTTCTTCTTAA
ACATTTTATATTTATGTTTGAAGCATGCCACCTTTCTTCACTTGCCAAC
TTGACAGATTTATTAGTTGACAACATCCGCTGATAGCATCAGTAATAAGT
TAATTGTTTTTGCACATGTAGCTTTAATTATTCTCATTATCATTTATAGG
AGTTATTCTTTGTAAAGGGTAACTGAGTTTTCCAAAACAAACAGAAATTT
GGGGTGGGCCCCATGGAGCGTGACTCATGAAATCAGATTCTTAGAAGGACC
TCGGCAAGTCTCTGGGTGCTGTTAATGAGCCTGGCTGGCTGCCAGGGGT
GTGTCTGCCCTTTATGAGGCCACCACTGTTCAAATGCTTGCCTGCAGCAT
TACTTGCCCTAGGTAGTGCTTGTCTTCTACTGAACTGTCAGGGATCCAATTC
TTTGTGGTCTAAGTAACAATACTCAGATTCACAAGGAATTGATTAATAAG
CCAGAATGCCAATGTATTACATTTTGTATGAAGACCATATTTACAGTGAT
TGTATCTGCTCAAGCTCAAATTAGGATTAGAGTTCTGACAAATACATATG
TGAGAAGTATGAGGTTAAATACTTGAAATTTGGACTTTTCTAGAAAATCT

FIG. 4 (25 of 61)

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GAATGTGATTGCCATTACATACCTTTCTGGGGATGATGATTCTTGTACT
TTTATTTTAAAAGACATAGAAAATACTTAAGAATCAGATTGCTTGGCT
GGGCACAGTGGCTCATGCCTGTAATGCCAGCACTTTGGGAGGCCAAGGTG
AGTGGATTGCTTGAGCTCAGGAGTTTGAGATCAGCCTGGGCAACATGGTG
AAATCCCATCTCTACCAAAAATACAAAAAACAACCAAAA
AGAATAAATTAGCTAGGTGTGATGGTGCCTGCTTGTAGTTCCAGCTACTT
GGGAGGATGAGGTGGAAGAATTGCTTGAGCCCAGGAGGTGGAGGTTTCAG
TGAGCTGGGGTTGCAACAGTGTACTCCAGCCTGGGCGATAGAGTGAGACT
CCGTCTCAAAAAAATACTAGATTGCTTTATTGCTGGTTTTCTTTCT
AAAATGAGATTGGGTCCCATCATCCCCCTGGCCCCATTGGTTAATGGTT
CCTCCTTTGTCTATTGAATAAAATACAGATGTCTGCTTTTGGCAACATGG
TTGAATGTAGACACTGCAGGGTCTTCCTGACTCAAATGATTTAGGCTTA
GATAAACACATTTGGAAATGCATTTCTGGATTAAACACCAAGGAAAGGAG
ATCTCTTTAAATCCCCCTTTCTGTTCCCCCTCCCTACCCCCCTCCAATTGG
GCTTAAGTAAGAAGGGTGGTTACCCGCTAGTAAACCCCTTCGAAGGGGG
TCTTCTCCTCTAAGGGAAACCTTGTTTTGACATTTGCTTCAATGGGCC
CTTGTATTTTGTTCCTTGCTAAACGGGTGCTAAACCAGGGGCCTCCTCTT

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AAGGCTTTTAGAATATTTGCACACTTTAGAAATGGAAATGTTTTTGGGGG
GCGAGTTGTCTTAATATTTCATTTTCTAGCTTGTGTGACATCCTTTTGA
AAGCAGCAATTCTGGCCTTTGTGAGAGATGGTGAATGCCTGCAGGTGTGT
GGACCAGTGGCTCCCTTCCTTACATGCACGGCCCCCAGCTGGGCCCCA
GCAGAGTGCTGTACAGAATAATTTCCAAGGGCTGTGTCTTAACCTTTG
GTCTTGTCCCCCATTTGCTGTAGATTTGGCCAATTGACTTCATAAGTGCCT
CTTATGAACATAGATGTTGGCAATGGAAGTTGAGGACCAGTCAGTGGTTG
TTTTATTGAACACACAGCGTAAATCCCAACACAATGCTGACCTAAGAGAA
TTCCAGCCACTCTGATTCTCAGTCTCTTTATATCTGAAAGGGTTCTGTTC
CACTTTTTTCCAGATCAAATGTCCCTGCAGCTACTCAGCAGAGCTGTCTG
CAACTTATACGTAGAAGAGGTAACAGTCCACAAACAGAAAGGCACAGGAC
GAGAGTGGTCTGGGTGATGCTTCCTGTGGGGGAAAAGGTGATGAGGGTGC
ATCTGCACACCTATGTTCATAGGTAAGTCTGGGAGGAGGTGACCTCCCCT
TTGGTTGAGGTGCTGAGGCGTCTTGTTAGAATGGCACTATTCCATTTATC
TGATGCAGTCTGTGGGAATTTTGTGGTATGGCCACCACAGGTACCATGCT
GGGAACAATGCCAGATACTGCCTGCTAAGCCACAGCATGAGTCACATGAG
CATTTGTGGGCTTTGGGAATAAAGTTATTGAACGATAGTTATCTGAAAA
GGAATTTAGGGAAAGGGGACTTTAGTCCAGCGAACAGTTTGCAAACCAGG
GGGAAGGCAGCCTTCAGCGTAAATGAAGACGTGTGTGCCCAAATAACA
AAGGGAGAGTTTGTCTTTTAGAGAGTAAATGTCCACGCAAGGTTCCACTT
AGGCAAATGAAAGATGCAAACTTGCTTAGTTCTGATTTGTTTACATTTGC
TGAATTCGGATTGGTCCGTGCAGGCTTTTCTGGGAATCCAAATACATGT
ATGACCTCTAGTCATACATGGCAAATGGCCGCTTGGCTCTAATTTGAATT
TAGGCCAGTTAGTCACTCAGGATTAACCTTTTTTCAGGGTTTACAGCTCT
GAACAATGGACTTAGACCTGCAGGACATAATCTGTTCTTAACCTCTGGGAC
TACCTGTGCCTTTTGAAGTGTGCCAGTGAGCAGCTGTGGCTCTGGGCCCCA
GACCCACAGGGCGATAAGGCACAGAGGTACGCATGGAGCAGGCTGTCTT
GCTGAGTGATCATGAAGATACACTTACATAGAGCAGCACTTTTCTTCCA
GTCTTTGTGATTTAACTCATTAGATCCTTATAACAAGAGTCAGTCCTCTA
TTTAACCCATGAAGCACAGGTGGAGTCCAAGCTTAGTTTGTGAAGGATGA
GCCAAAAGGATTCTTCTCTTGTAGACCTCAAGCTCAGCTCTCTCCATGGG
CCCTGGAGTAGGTGAGAAGGCCTCTGTCTTCCAGAGCCCACTGCCAATCA
TCTACATTTTCTGTTAGCCCAATTCTAGGACATTGCTTTACCAACTGAAG
GGTGAGAACTATCATAAGTTATAAAAATCAATTGAAAAACAAAAGGTAC
AGAACAGAAAATAAAAGATGAGAATCTATTAAACATAGTGATGTTACTGG
AAAAGGGGGTCTCAAACCAGACCCCAAGAGAGAGTCCTTGGATTTACAC
AGGAAAGAACTCAAGGTGAGTTGCAGGGTGCGGTGAATTGAGAGAGTTTA
TTGAAAGCTATTCCATTACAAAGTAGAGCATCCTCAGACAGCAAGTGGAG
GAACATGCCATCATTAAATTTTTCTTATATAGGAATCTTGTCTATATAAA
GACTAACTAAGCTGTGGCTATGTGTGGGTGGGCCGACAGCATGAAAACA
TTTATTCTCCTATTGATTTAAAGAGAACTATCCTTGACATTTTAGTGTGT

FIG. 4 (26 f 61)

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TTAAGTACATCAAAGCA1AACTATAATTAICTTGAAAGCATATATTTTAA
TAGGGATTGGGACATCTGGGCTTTCTGTTGTTGTAGAAGTTTGTCTTGC
AGGGATTACCAAGCCACTTCCTTAGCTGTAAACATCTTAGGGCCATGGGT
CCTGACTGGCAAGGAATGTGTCTTGCTAGTTTTTAAGATGGGCTTGATTG
AAAATGGTGTCCATCTGGCTCTCCTAGGCTCCTGCTTTCCTAACAGTAAG
GGTAAATGCTATGTTATGAAATGTCATTTCTGCCTTTAGCTTGCAAACCTC
TTGATGGTGAAATTCTCCTGTCCGTTTTTCAGTGGGGTATTTATTCTGCAT
CCACGTCTTCACAAGGAGCTGAAAACAAATTGGATGGAAGCAACTGGGTT
TTATGGGACACGTTAATGTTTTAATGTCATTTGGTGTGGAATTCAGATGT
CCAAGCAACATTTTACACTACAAATCTGCAACTTTAATAATCACTCAAAG
TACCTGAACCTCAATGCTTTCAGACAGACTTGGTATAAAGCCACCACCTC
TTTCTATTATGGCAGCCCTATCCTGAGGACACAAATTTCTGCAGGGCTTC
TGGCATATCTCTGATTAAACAAATGTCAACAAGGTTAAAACAAATGTCAT
CTCTGATTTGTTTGTGTTTTAAAGCCTGGATTTACTCATTGAATATTTCACT
CCTACTAGCATGTCTTGTAGTAGTTTTCTTCAGGGACCCTAATTATTGCT
ATTAAAAATATGTGTGCAGCTACATGTTTTTTTTTTTATCAATTTGCAATG
AAAACCTTTAATTGAATAATCTATTAGTGTTATTATTTGAAAGTGAAATCT
TTTCCTTTTGCTTTCTTGTCTCACACATAGTGCAGACAGTTTCCACACG
GGCTCATAAAAGGAATGATTCTGCCTTGTGTGAACCTTTTGCCTTTATTG
TTAATTGCACCATTTTGTGACTGGCTTCTTGACCCTGTTGTAACCAAGCT
CATAATGTACATTATTTCTTATTTTGCAGTTGTAGACACTTGAGGAAGTT
CCCATTTCTTGTGTTCTTCTTGCTTTTGTTCCTGTGATAACTTTTTCATG
CAGACATTTTTTTTTTTTTTTTTTTTGGAGACCGAGTCTTGCTCTGTCATC
CAGGCTGGAGTGCAGTGGCATGATCTTGGCTCACTGCAACCTCTGCCTCC
CAGGTTCAAGAGATTCTCCTGCTTCAGCCTTCTAGTAGCTAGGATTGCA
GGCGTGCACCTACCACACCCAGCTAAATTTTTCAAATTAGCCACCCACCT
GGCTAATTTTTGTATTTTTTAGTAGAGACAGGGTTTCAACCATGTTGGCCA
GGCTGGTCTCGACCAGGTGATCCACCCGCTTAGCCTCGCATAGTTGCAG
GTGCTATTCTGAGCTCAGGGCTCTGGCAGCTACAAGCCCAAGATGCGGTC
TCCAACATGTGGCCATTCAATGTCATGGCGCCCTCTACTGGTCCTGGGAA
GCGCAGCTCTGCCAGTAGCTCCAGCAGGGCACAGCTGTTAAGTCGTGATG
TTCTACAGGTGACCAAAGGGCAATCTCTGGACTCCTTAGCCGCTAGGTCC
TCTCTGTAGCAGGACCCAGGAGAAGGCAGGGGCTGAGGATGGCTCTCTTA
GACATTTGTGATGAACCAAACGTGTGTCATTGATGAACTTCTGTGAGCAA
GCAGGTGAGTAGAGTTGGGTTATAAAAAGTCTTAGGGTCTCACTACAGAG
ATGGACTTGCTGTGTAGATGGTGCAGAGCCGCTGAAGAGTTCTACTTGGG
GTAATGGTGTGATTGGGTTTTCGTTTTAGGAAGATTTCTTGGCCAGAATG
AGGCGGGCAACCCAGAGCAGGGAGTGGCCACATGTGGGTGTGCAGTTATG
GGCCACTAATCCAGGTGATAAATGGTGTCTCTGAACTTCAGGTGGGGGTG
CCACATGTCTCCATCTGCTCTGTACCCTTGAGACTGGCCTTATGGGCTGC
CTTAGTGGTCTGTTGTCCTCTATCTCCTGGTTGGGCTCAGGCAATGGGAG
ATCAGAGGGAGGAAAGAGAGCTTGGTTAGAGTGCACCCGCGCCCCCTCAG
GTTGGCAGTGGCCACATTCCTTATACAGAAGGCCACAGTTTCTGTGAGT
GGCCCTCCACAGCCCCAGCTTCTCAGTGGGCCAGCCACCTCCCCATCC
CTTGCTCCTCCTCCTCCAGAGAGGGTGTGGATTTCCACTGTCAGCAGTG
CCTGGAGCTCCACCATCTCCTGCTGCTTCTCTGGACCTGCCTGCAGTTT
TATAAATAACCTTTCCTTACATTACCTCTAGCATGCACCTTTTGTGTGTA
TACTCTGCCCCCTGTGAGCACATGACTCATGCCAAAGAGTTTGAATTTTT
TTCTCCAGGCAACGGGAGGTCAATTGGAGGATTTTAGACATTGAGAACAGA
TGTGTATTGTGGAATATCTGTCTGACTGAAGTGACCAGGATGGTCCAAA
AGAGCGAGAATTTGAGGCAAGCAAACCATCAGCAGGCCAGCAGCAGAAAT
CCAGGTCATAAACAGGGAAGCTGAGGCTCACAGGGTTGGATCAGGGAATG
GGAGAGGGAAGCCAAACAATTCATGAGCATGTGAGTTGCACATATGACT
TGGTAACTATTTTTATTTTTATTTTTATGTTTTGAGACAGAGTCTCGCTC
TGTCACACAGGCCAGAGTGTAGTGGCATGATCACAGCTCTCTGCAACCTC
TGCCTCCTAGGTTCAAACAATTCTCCTGCCTCAACCTTCCAGGTAGCTGG
GACTACAGGTGCGCACCCTACACCCAACTAAGTTGTGTATTTTTAGTAG
AGATGAGCATTACGCTGTTGCCTTAGACACGG

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AATATTGATTATTTGACCAGAAATTCATGCAGCTAACCGTGACCCCTGGC

AAAATAAAATAGTGTAT...GTACGTGCAATATACATGCAAAGAAATGAG...
GAAACTAGAAGGATGTCAATCAAATGATAACATGGTCATCTTGGGGTCCG
AGTACATTTGGGGATGAGGGGAGCTGTAAAAGCAGACTTGGACCTTTTCT
TCTACCAGTACCGTGTCTTTTGAATTTTGGAAAGAAAAAAAAAACTCAG
AAGGAGGAGAAGGAGCAGGAGGAGAAGAAGATGGATCTTAAGTGATTTGC
CCGGGAGCACCTTGAGAAGGTGAGATTCAAGTCTAGGTCTAAGCTTTCTA
ATTCCATGAGTGGGAGTGACCCACGTCCAAGAGGAAGCTCAAAGGAAGA
TGTTCTCCATCATCTCTTGCTCATCTAACAGCATGCAAACACATCCA
ATGCAGCTCAGAAAACCTCCCAAATTGCCAAATTTTATTGGAAACACTTAA
TGCTGTGGTTTCCAATTTCAACTGTAAAGTAGGTATGTATGCCATTGTTA
CCATTAACCTTCTCAGAAATGGAGAGAGCTCTCTTTCCGCCTCCTCCCCCT
CTGCTGTGGCTTTGGTGAGACGTGCACTCAGGCTCACCTGTCTCCATGAT
CTCCAGTAAGTACACATGAGCAGAGAGGCTCAGCTCAGCTCTTCCTGGT
CCCACCAGGGTTGATTCTTTGAGAATTCTAGAATGCCACATCCTAGGCCC
CCCAAAGAAATCCTGCATCTTACCCCCAGAAATATGAATCATAGCAAATT
TCAAATCAACCATCGTTTAAATACTCACAGACTGGGCACATCCAAAACAT
ATTTTCAGTTTTTACAACAGTGCCTGGTGCATATCGGCACATTTTGTGGAA
GCAATAAATCGACACGGAGCTGAAACACAAACAAATGCCAAATTGTTTTT
ATAACACCTGATTTTCTTTCTGTTTCTTTATGCAGTTTAGTTTTGTTTTG
CTTAACTCTACCTCAGACCATAGTCTGGTAAACTCACCACCCAGAAGCTC
CCTTGAAATGTGGGTATGCAGCCACTAGGTGGCAGGAGAGAGTTTTCTGC
CTGGAGGGAGGACAGCCACTCTGTCCCCGGGTGAGGCCAGGGCCACCCTG
CTACCTGCAAAATTAGCATGGGGCTTTATGAACCACAGCTTCCTAATAAA
CACAGGATCTGTTTGATAGAGACTCCAAAACACGCCTACCTAGTGATGAA
AGACTCAACTTCAGAAGAAAACCTTCATGGCAAACATCTTCAGAGATGTT
TCCAACCTAAGGTTCTGAACACAGACGCTTCCCCAGAAAGCCATTGTTTC
TCAGCACCTGGGAGCCTTGCTTTGCTTTGCTTACAGACTCGCTGTTCTTA
AATCACTGCCAAGATAACATCTGTCTCTTCTCTTACCCTCTATTTTGATA
TAAGGACTCCTCACTCTTGTTGCTTCTTATTGGCTACCTCTCCACAGGGA
GAAATCGCTGATTTAACAGCAGTCAATATCCCAAATCTGGAACAGGGAAC
AGGGAAGCATTTAAAAATTGGAGAATTTAGGCCGGGCACAGTGGCTCATG
CCTGTAATCTCAGCACTTTGGGAGGTGACGTGGATGGATCACTTAGGAG
TTCGAGACCAAGCCTGGGCAACATGGCGAAACCTCATCTCTACAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAACCCAAATTAGCCGGGCATGGTA
GTGCACACCTGTGAGCCCCAGCTACTCAGGAGGCTGAGGTGGCAAGACTG
CTTGAGCCCTGAGGTGAGGCTGCAGTGAGCCGAGATCACACCACTGCAC
TTCAGCCTGGGCAACAGAGTGAGACCTTGTCCCAGATAAATAAATTAAAT
TAATTTAATTAGAGGATTTAAGGATTTTCCCTACAGACACCTCCTTATTT
TCTCTGGCCTTTTCTGACTACTCTCCCTAACTCCCTGCTCCTCTGGTCTC
CCAAAACCTACTCCAGAAAAAAAAGGGGGGGAGGGACTAAAGGAAAGCC
AGGTGACAGTGCCAGTGTGACAGATGACAAAGCATCTGCCCCGAACAAACC
GTAGGTCCCTGAACTTTCTCCAAGACCTGTCTGTGGACTTACCTATGAAA
ACCAGTTTTAGCAAAAACCTCCTAAGCCAGTTTATCAAGATCCCCTTAT
CCTCAATATCCATCTGATTGGATTCTTCATCCCCCACCATTCCCCAGTGA
TGTCACCAGGCCTTTCTTCAGCAACAGTAGTTAGTGGGTGTAGCCAGGAC
GCCCCCTCACCCCTGATATGCCCTTTTAGTAATTCTTCATCCACAGGTTT
CCACCCTGCTCCTAGGCTATACATTCCCATTTGCCCATGCTGCATTTCGGA
ATTGAGCCCACTTCTATACTGAGGTCTTACTTCACCTCTCGCCATAGTCC
TGAATAAAATTGGTTTTTACATTTAAAAACTGTCCAGCTCTGGTTGTTCC
TTGACACAGGGTAATTTTTATTCCATGTGATAGTTTGCCTTACCTCAGCC
TACACCCCTCAAACCTGCAACTCTATATTCAAGAACCAGACAGCCCTTTC
CAACAGATAGGAAGAGGCTGCCCTGGTGCAAAGGAAGAGGCTCTGGGAGG
AAGGAGAGAACCCGAAGGCTGCCCCCTCCTCTAGACTGAGCTCTGGGATG
GGTGGACGATAAAACCCAGATACGTTTAGACATCTGAGCGTGGAGAGGAC
TTTGCTTTGCTTCCACAGGGACCCCAAGGAACTGCAAGCCCTCCAGAGA
CTAAAAACAGCAGAACAGCAAGAAATGGCAGCAAAGGTCTGGGCAGAAATC
ATCCTATGTGGGCACAGACACAAACAGAGTCCCCTGTGGCCCCAGGAGAG
TTTAAAGAAGATCCAGAGGCTGTCCTATTCCATATCTCAGCAGAGACAGG
CCCGTGAGCCTAAAAGCTGATCATTAGGACAAGAAGGACACGAACTGTCC
TGCAGCGTGAACCGCGTGGAACAAGGCCAATCACCAGACACCAGACCAGC

FIG. 4 (28 of 61)

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CAGACACAGCCCCGCGAGTSCCCCAAGACCACCACGGACCCATCGCCCCCTC
ACCAATAGCTCCAGGCTACATAGACCCCCCTCCACTTCATGGATGTCCTCA
GAGCAGAAAGGGGAGGCAGGAGTGGAACCCCTGACTTGGTTCAGTTGAAAC
ATAAAATGACTGTACTATTATTGAATTGCTGAAGTTTACGTGAAAGAAAT
GAGATTTAGTTTTTGGCCACAGTGCAAAATAAGAAACGAGGCTTCAACTG
AGATTAAGGTGAGTTATAGGAAAATGTACTCCCTTGAAGGACCTGTGAAG
TGTTGTCGCTATGAGAAAATGACCAGAATCCACGTTCTTAGCTGCGGGAC
TCAGGCTGACTCCTGTTTCTGGAGCTTGACAAAGGGCAGGGAAATCCCT
GTTTCAGGCACAGTGATTTCAATGTTTAAAAGAAAACAGGTGGGCCCTGG
CAATCATGATAACATGTCATAAGTTTACATCTCTGTGAGGCAGGTAGTGT
AATCCCCATTTTGCAGAGGAGGAAACCGAGGCTGAAAGCAGCTACATGGT
CTCTTCAATGTGGCCCAAATGTTGGAGAACAGAGCTTAACTGAATCAGCA
ATTCTATACTTAGAACTGACTCTCTCTTTATTATATCTCACTACTACCTT
GATATTTGAAATATTCAACTTTTTTCAATCAAAAATAACAATAATTTAG
GCATAATGACTACTATGTCATTTAATTTCTTGCTGATATTTCAATATCCC
ATGCCAGGAATATTGAAAGCTCAGCTCCTTAAGAGCTGACTATGGCATCA
ACTCCCAACAACCATCCTTCCAGAAATATTTTCCCCTTTCTTTTGTATA
GAGTGGCACTGCCCTATATGGTGACCACTTGCCACATGTGGCTGTTGAAC
ACTTGAAATTGGCTTGTCAGAATTGCAGTGTAAGTGTAACACATACC
AAATTTCAAAGACATGGCACATAATAAAAAATGTAAATATCTCATTAAC
AATTTTTATATTGACTGTGTAAGTAACATTTTGAATATATTGGATTAAAT
ACATGGATGATGCCCCAACCCACAGTCCCTTATCAAGTCTCTACTTCA
CATTTTTGTACTTCTGACTTAGAAATAGCACTGGCGTCTAAGAGCCTATT
AATGTCGTCAATAGGTTCTTGGAACCACAATTTTAAACAAAATGACATA
TAAGAAAACGAATAACATTGAACAAAATGACATTATTCGAGGACCTGCTG
CATGTTGTTTCACTTAAAGTCAGTGTCGAAGAACCTATCAGTGACATTTA
GTGAGGACTTGCTGTCCTTCCCTGTTTACAGGAACCTGGGCAAGTTACTTA
ATTCCTCTAAGCCTGGTTTATATCCCTGCAAAGAGAGAAGGATAATAATC
ACCAGTACTTAGTGATGTCGTAAGGAGAAAATAAAATAATAAATATGAAA
TGGCTGACAGTGTCCTTGTCACACAGAAGATGTGTGATCCACAGTAGCTG
CTATTGTCTGCCTCACTTCACTAGTAATGGTCCAGGGAGGCCTTTAATGT
GCATGGTGCAGTACATTACATGTTGGACATGGGTGAAGGGAAAGACCAG
GCTCATCTAAACACAATAGGATGCTTGTTGGTGTTTTGAGGAGGAATCAAG
GACTAGTTATCCACAGCTGTAACATGCATGGATCAAAGAGATAAGGCAC
ACAAAAGACTTTGTGAGTAGCAAAGCATTACAAAATGCAGAGACCAGCTG
TGGGTGGTGGTGAGTCAGACCCAGCTTCCCTCTGTGCCTGGCTGAGTGGT
TCTGGGCAAGTCACGCCATCTGTCTTGATGCCCTTCCCCATCTATAGAGA
GGGAGCAACTGAGGCCCCCTCCAATACTGAAGTCCTTTATTTCTGCTACT
TTAGAAATATCCACATTTTTTGGTAAATTCAAATGATCCAATGATTCCATT
TCCTAATGTTCAAACTAGCCCCAGAAACATCTAAATGAATCAAACAAAT
AAAATATTTATTGTGTATGTTTTGATTGCTGAACTTCTATTTTAGCAAC
ACACACACACACACAGAACCCATAAGCCTTCATCTTTCCTTGGATAAA
CGAGCCTTCCTGTCTGGCCATTTAAGTCACGATTAAGTAAATGATTTCCA
ACTCGCCTTTTGCAGCAGTTCAGATGGGTCTTTCCTGCGTGGCAGTGGCC
CTCCTGACTTATGATTTCTGTGTGTGCGGCCTGTTACCACTGCAGCTTAA
CTGAGGAACAAGAACAACACAGCTTCTGACCCCAAGAGACTGTTGGAGG
CAAAGGCTTCAGTCCAAGAACCTCACACGTGGGGAGCCCGAGAGCCAG
CCCTGACCTTTTCTCCAGTAATAACATAAGAAACAACAGGCACTGGCCTT
ATTTTGGATACAAAGAGTGGTGCTTTTCTTAAATCTTCTTTAGTCAGG
GCTACCCCTTCATGGACGCCCCAACATCCATGGTTCCTGCTTGAGTCCCT
GCTTCCATATTCTGCACTTCTCACTTGAAATATCCCTGGAGTACGTTAA
GCAGCCAGGTTTGGAAGTTCTTGCTGTGCAGGCGGGTGTGTGCATGTCCT
CTCTCTCAACAGGACACAAGCTCCCCAAATCAGACGGTATGCCTCCACGC
CCCTTCCCAAGCCTCCCCAGCAGCACCGAGCATGTGAGGGGAGCTGGGGC
CCAGGCCATGATGGGAAGCACTCTCTGCCTAAAGACTAGGGTGATGCGCC
CTCAACTGTGGGAATGAGCCCCAGCTCTGGTGTCTGCCTCGGTTTTTCTT
CCTGGACAATCAACATGAACTCCTCACCCCTCTTATCCACTTTGCATAAA
CTGAAAATAACAAACCCAGGGCTCTTCTGTACAGGAAAGGGTTTTTTT
TTATAAAATTAAACAGAGATGATTCAACACACCCAGGATATAACACATGG
GCCATGAATCAAGGGCAGCATTGCTCTGGTCAGCCTGTTGTTTGGGCCCC

CTTGGCAGGGCTCTCCCCA GAATCTTCCCCTCTTGACTCCCATCANACA
GCACTCCANCTTTGTGTTACAGGCGATAAATGGGAAAGGGGTAAAT

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CATTCTTAATTAGAGAAACGCTCATTAACTAGACACCCAAATTCTCTGG
GGGGGGATCATTCTTACAAGCATGCCCTTCTCTCTTAAAGAGAGAGCACT
TTTTTCGCAAATAATGCTGCCATGAACATACGGGGTGCATGTATCTTCGT
AATAGAATGATTTCTATTTTGGGGGGTATGTACCCAGCAATAGGATTGCT
GGGTCAAATGGTATTTCTGGTTCTAGATCTTCGAGATCTTCCACACCGTC
TTCCACAATGGTTGAACTAATTACATTCTTACCAACAGTGTGAAAGCAT
TCCTATTTCTCTGCAACCTCGCCAGCACCTGTTATTTCTTGACTTTTTAA
TAATCGTCATTCTGACTAGCATGAGAGACAGTATCTCGTTGAGGATTTGA
TGTGCATTTTGTCTAATGATCAGTGATGTTGAGCTTTTTTTCATATGTTTT
TTGGCTGCAAGAATGTCTTCTTTTGAGAAGTGTCTGTTTCATGTCCTTTGC
CCACTTTTTAATGGGGGTTTGTTTTTTCTTGTAATTTGTTTAAGCTCCT
TATAGACTCACAATAACAAAGACATGGGATCAACCTAAATGTCCATCAAT
GATATAACGGATAAAGAAAATGTGGTACATATATACCATGGAATAGTATG
CAGCCATAAAAAAGAATGGGATCATATCCTTTGAAAGGACATGGATGAGC
TGGAACCATGATCCTCAGCAAACATGCAAGAACAGAAAACAATTGTTG
CATGCTCTCACTTATAAGTGGGAGCTGAACACTGAGAACACAGGGACACA
GAGAGGGGAACAACACACATTTGGGGCCTGTCAGGGGTGAGGTGGGGGAG
GGAGAGCATTAGGAAAAATAGCTAATGCATGCTGGGCTTAATACCTAGGT
GATGGGTTGACAGGTGCAGCAAATCACTGTGGCACACATTTACCTATGTA
ACAAACCTGCACATCCTGCACACGTACCCAGGACTTCAAATAAAGAGA
GACAATACTTCTCCCTTAAGTGTCTACTGTTGCTTTGCAATAAAAAETTC
CTGCCCTTTCACTTCACTCTGACTTGTCCCTGAATTCTTTCTCGTGATGGT
GTCAAGAACGTGGACACTGGCTGGGGCTGGGAGACTCACCAGCATCCGGAG
ACCCTCCTGAGCCCTCCAGCAATACAACCTTTGACACAAACTATGAAATCA
CAGATCCAAGAAGCTCAAAGAACCCAAGCACAGGAAACATGATGAAACTA
CATGAAGGAACATCAGAATTGAATTGTTCAAATCAGTGATAAAGAGTAA
ATCTTAAAGCAACCAGAACAAAATATCCATCATATACGCAGAAATAAAG
ATAAGTATGACAGCAGATTTACAAATAGAAAAAAAACAAGTGCAGCAAC
AGAAACAAACTATCAATCCATAATTCTATACCTAGTGAAAATTTCTTTCA
AAACAAAGGTGAAATAAAAAAATTATTTTCAGGAATACAAAAGCGAAAAA
ATTAATCACTAGCATTTCATCACTGCAAGAAATGTTAAAGGAAGTCCTTTA
GGCAGAAAGAAAATGATACAAGGTGAATATTTGGATCCCTGCAAGGAACT
AAAAAGATCCAGAACTGATAACTTAATGGGTAAACATGTAATTTTCATCA
ACAAGTGAATGAATAAACAAATCATGATATATCCATATGATAGACTACTA
CTTAGAATACAAAAGAAGAACTACTTATGCATGTGATAACATGAATGATA
TTCAAATTTATTATTGAGTGAAAGACACCAGATCAAACAAAGTACATAC
TGTATGATTCTGTTTATATAAACTCTATAAATTGCATGCTCTTCTATAG
TGACAGAAAGAAGATCAGTGGCTGCCTGCAGACAGGAAGAGATTACAAAC
GGAAATGAGAATTCCTTAAGAGATGATGGACATGCTCATTACCCATCATA
TGTATACAGCCATAATGGTTTTACAGATACATATATATGTACACGCCAAC
ATAAATATAAGTTATCAAATTACAGTAAGTTCTGACTTAATGTCACTAGG
TTCCTGGAACTTTGACTTTAAGCAAATGATGTACAGTGAAACCAATTT
TACCATAGGCTAATTGATATAAAGATGAGTTAGGTTTTTGGTTTTTTTTT
TTTTGACATGAAGTCTCGCTCTATCGCCCAGGCAGGAGAAGAAGAGTTAG
GTTTTACAGCATGTTTCTGGTCACAAGAACATCATCAAACCTTGTAATAA
AGGCACAAAACACTTCTAATATTAAATATCAAATAAATATGAGTTATAC
AGAATTTAAGAAAGATTAATAAAAACAAGTAAATCATTATTTATGGGAT
TTTTGGTAATCAGTGAGTTATGTGGTCATAGTGGAAGTGGGTAAAGTCAA
GAAATAAATGTTTGCAAAACAAAAATTTTAAAGATCCTCTCCTACCACCA
CACAAAAACAAGAAACACGGTGGGCTCGCTAAGCACTTTTGTACCACT
CGTATCTTATGCGTTTGTATGATTATTGTAAATGCTTTATGATAATTTTT
AGAGACAGGGTCTCACTCTGTGTCTCAGGCTGGAGTGAAGTGGTGCAATC
ATAGCTCACTGCAGTCTCAACCTCCCGGATTCAAGAGATCCTCCACCTC
AGCCTCCAGTGTAGCTAGGACTACAGTTGTGTGCCACCATGCCCATCTAT
CTTCTTTTTTATTTTTTGTAGAGACAGGGGTGTGCTTTGTTGCCCAGGC
TAGTCTTCAACTCCTGGGCTCAAGCAATCCTCCTGCCTCAGCCTCCCAA
ATGCTGGGATTTCCGACATGAGCCAGCAGCACCTTGCCCAGCATTTTATT

TCATAATAATTATAAGTCATTCCTTCATTCATCTTACAACCCACTTGTTTC
CAGTTCAGGATCTCGGGTGACCAGAACCTATTAACGTTACGCACAAGTC
AGAAACCAGCCCTGGACAGGACACCATCCTACCGCAGGGAGAACTTACAC
ACCCACACTCACTCAGACTGGGACCATGCAAAGAACCTAACGTGCACTTT
GGAATGTGTGTTCCATACCCACTAGAACAGCTAAAATTTAAAAGACTGAC
CATACTTGAGTGTGTAACAGGATGTGACACAATAATCTTTTAAGCGCT
TCGCGTAAATGGCACAGCCGCTTTGGAAAACAGTTGGCAGTTTTTCAAG
TTAAATATACCCAAACTCTATGATCCACTTCTCAACAATCAAACAAGAGA
AATAAAAGCAATGTCTACACAAAGATGTATACACAAATGTTTCATTGCAGC
CTTAATTATACTAGCCCCAAGTTGAAACAAGCCAAATGTCCATTACCAGA
TGACTGGAACATACAAATTGTGGTATATTGATACAATGAAATACTACTTA
GTAATAAAAAAGAAAGAGCTATTAACATAAGCAACAACATGGATGAATCT
GAAAACAATTATGCTAAGTGAAAACAGCCACACAAAAGTTACATACTGTA
TGATCACATCTACATAAAATTACAGAAAAGGCCAACTAATCTATAGACAG
AAAAGCAGATGAGTGGTTACCTAGGGATGGGGCAGAAGGGACGAAAGGAT
GGATTGCAAAATAGCACAAAATATTGGAGGGATGACAAATATATTTCATT
ATCTTGATTGTGGGGATAGTTTAATGGGTATATATAGAGATCAAAGCTCA
TCTAATTATACACTTTAAATATATGTATTTTCATTGTGCATCAGTTATTCA
TCAACAAGACTATAAAATAATATATGCCTACATATTTTTAAATATTCA
AAATCTCACAGTTATATACATAAATGCAACTGAATATGTATTCAGATGTT
TTAACAAGCAGAAAGGACTGATTAAACTCATGACAGCGGCTGTTTCTGGG
AAGGGTGTAGGAGACAAGAGATGGAAAAGAGGATGAGAGCCAGAAGAGAC
CCTTGTAATGTTTCTTTCTTTTAGTAAAAATATATTGACAGTTAAAGCT
GAGAGGTGAGAATAATAGTCTCATGGCTTTTGTGTCCTTAAATTTTACA
AACTAAGTGAAATGGGAGAAAGCAAAAAAATAAACTTAAATAAATGTTAT
ATTGCCCAAAAAGAGATTTAAATGGAGGTAGACACATGAGACTTACGT
TCTCAAAAAGTAGAATCTGCAGGGAAGTTTAACTATAAAGAATTAA
AATCTAGCTTCTACCAGCCCAAGCCTAAATGTTCTGCTTTATTCTTCC
TTATTATAATTCATAGGTAATATATTTTATGTTTGCAAATGAATGCAGTG
ATATTAGATCTCTAAGAGGTGCTAAAAATGAAAAGTACATATTCCAATTT
TTCCCAATTTTCTTCTCTTTCCATGAATGAAAATATACATATTTGATG
ATTTCCAAGTTTATACAACCGATCTTTCTCTTAGTTTTCTCTTACCAAAT
TCCCTCCCTCACTCAGCCACCAGCCAGTCCAAGTGTGCTACCTGCACAGC
AGCCCTCATACCATCCACACTCTCATCAGGATCCTGCCTGACCTGCGAGG
AGCAGCAGCAAGAAGGAGACAGAACCTCCACGCTGAGCATCTCAGGGCTT
TCTCAGAGACTCCAGAGGACCCTGATAGGGACAGAGCCTGGCCAGCAATC
CATGCTGCCAGCTGTATGATTGTGGGCATGTAAATTCTCAACTGAAAATG
GGTGTAAATAACATGTTCTTCCAGAATGAGCTTTATGAAGATCATAT
AGCTGTTTGGAACTCAGACAAGCACTGGTAGGAATACAAACAGGGGAGCC
AACAGCCTATAAATAATACTTTAAGAAAGGGCATGAATGTAATTACTTAG
GAACAAAAGGCAAAGTGGAGAGATGCCTAGGACTGAGCTGGACAAGCTGC
ACCCTTTAGTGGCTCAGCCCATGGGCTGACAAGGAAAATGGAGGAGCTAC
CAAAGAAGGTGGAAGGATTCTGGGAGAGTGGCCCTCACCTGCCCAGGGC
AGGGCTCAGTGGGAGAGAGGGAGATCTGTTATAAATGCTGCCAGGAGGTC
GAGTCATGTGAGAATGTCCATGTGAAAACATCCACTGTGTGTATCTAAAG
AGAGTGGCTGTAAAACAGGTCAGGGTCAAAGGTCTTATTGTCTCAGATGT
TATCTGCATGCATTGTCTCACGACCAAGAAAATAAGGAGCATGGACACA
AAGGGTTAGGTTGAAGCAAAAATTTAATAAGTGAAAGAAGAAGGCTCTCT
GCAGTGGAGAGGGGAGTCTGAGTGGGTGCCACTTTGACAGCTGAATCCA
AAAGCTTTTATAAGAACTCTTCTCATATCTGCAGCTGTTTGAGTAACTT
CTCTTACCTATAAACTGTCTGTATAACTCTCCCTTATCTATGCAGCTGT
GGGATGTCTCCAGGTAAGCATAAAGTGTAGCTTCTCTTGTGTTGTATAACT
GTGGGTTTGTGTTTAGGCAAGCCCCCATCCCTCCCTGTGTAAGCTCCCAT
GGAGCCCACCATGTGCATATCTGAGAAGTGGAGGAAGCTTTCTCTGGGAG
CTCACTGATCGTACAAAGAACAAGAGGCTTCTGTGCCGCTTATCTATTCA
GGTGCAGCCTGAGTTTTCCCAGGCTGCTCTATTTTGCCTGTAGCTATG
ATTTTTCAGGCAGGCTGCTTCTCTGAAGACTAGCCTTAACTGTCTACCTA
TCAGATTTTTCTTTCTTCTCCCTCAGCTGGTTCCCTCACCAAGGCTG
AGCAAGTGAAAAGGAGGGGCAGGGCAGGCCAGTAGTGAGCAGCAACAAG
GAACTAAGACAGCAGAAACCACTCTTCACACCTGGGTTGAAAGGGGTGGG

FIG. 4 (31 of 61)

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GAGCCAGGACTACAGC1 CAGGTAAGAACATAGGTAAAGAGATACTGTTGT
TGTGTTGTTTTTAACTATGAGAAGCATTGAGCTTTAAATTTCTACAGGAA
GGATCCAGTTCAGACAGGAGCACCCAATATTCAGAAGAGAAGAACATGGT
GTAAAGGTCCTGGGAAGGCTGAGAGGATTGGGACTCAGAATCCAGAGCAG
AAGCCGTCTGTGAACAGAAGAAGGACCTCCCCCAGTGTAGCAAGAGGGAG
GGAGGAGGGACAGATGCCAAGATGGTTCAGGAAGAAGGTTTGGTGGTAAA
TGTGAGGCTGTGCTCACCTGCTGGCTTCAATTTTCTCTTTAAATGTCAG
ATGGAATCATTGATGAAGGCCATGCCATGCAATGAAATGGCAGTCTGAG
GCATGGAGCAGCTCCAGCTTAGCCCCGTGTTTAGGGTAATTATGGCTCCAA
CCCAGGAGATGAATATGACTAGGGAAAGTGAAGTCCAAAAACAAATGGTC
TCAAGTTGACTGTGAGTCTTCTGGGAGGCTGAGACGACAGGTGGGGTTGA
CAAGGGAAGGGGAACCCACCTGCTGAAAAACATCAGGCTGTTGGCTGGGG
GAGGGGTGAGGCCTGTGTTGTAGAGATGGATGGATGCCTAAAGTTGGGTA
AAGGTTTCAACTCTACCCTCTGCTGGGTGTGGAAATAAACAAAGACCACC
CAAATGAGAACAACAAAGACTATTTATCCAGAGCTTGCTCTGACAAGGG
AGTCGGCAACCATCACTTGCTTGGCAGAGACTCAGAAGTAAGCAGGGGAG
AAAGCCTCATAGCAGAAAGAAGGGAAGTCTTCATGTATGCCCTGAGTGGC
AGCTGTAGATGTGGGTGAGTTGCAGGTGGCTAACTAGAAATGGGGGACTC
CTGTGTGATTGATTAGGAGCATGTTTGGCTTTCTCTGGTTGGTCCTACAT
TGGAAGAGGGGAACAAAAAATTTAGGGCAGTTGTCAGTTATTAATCAAGTG
TTGGCCATTTTTGACTGACTGTTACAGGAGTGACTGGCTCCCTGGATTGT
TTGCTAGAAATAGTGGTCTTCACTTCCTGCAAGTCTGACTTTCTGGTAAT
AGGCTTCCTGGGTGGCTATTGTGGATAATAAGTGGGTTCCTGAGCTGA
TTTCTGCAGATTGTGGATCAGAGTTATTTTATATAAACAGTCTGACCATT
TTCCACTGGCATATTCCATCTTCCAAGAGCTGGCCAAGCTGCTGTCTTAT
CTGTCTCCCCCAGCCCCTCCACTCTGGCTGTGAAAATACAAGCCACTAGG
TGAGGAATGGGGACAATTGAAGACTGAAAGCTTTTCTTTGCTGGGTTCGC
AGAGCTGAGGAAAGAAATGACAACATCCAAGTGTCTGCCCTGGGCCAGTT
TTAGGACTGTAGTGGTAATGCAAGGACTGTGTGAGTTTATATTTTCATTT
GTCTCTCTAACTAAGGTGGAAAAAAGAAACAGAAAATTGTCTGTCTGCA
GTCTCTGCAAAAGTCTAACACTGTGCTTCCCAACATTGCAGCCATTAGCC
ACAGGTGAGTATCAAGCACTTTAAATGAGACTGGTCCAACTGAGATGTG
CTCTGAGAATAAAACACACAGCAGATTTCAAAGACCTAGTACATGCCCTG
ATTTCAAGCTATATTACAAAGCTGTGGTAATCAAAACAGTATGGCATTGG
GAAAAAATAGACACATTGGTCAATGTGACAGAATAGAGAGCCCAGAAAT
AAACCCGTGCATGTATAGTCAACTAATCTTTGACAAGAGTACCAAGAATA
CACAATGGGGAAAGTCTCTTCAATAAGTGGTGTGGGAAACTAGATATC
CACATGCAAAAGAAAGAAATTAGACCCTTGTATTACACAAAATCTAAAT
TAATTCAAATAGAAAAGACTTACATGTAAGATCTAAAACCATAAACT
CCTAGAAGAAAACATAGGGAAAGAGCTCCTTGACACTGGCATTAGCAGTA
ATTTTTTCAGATATAACATCAAAAGTACAGGCAATGAAAGCAAAAACAAGT
GAGAGTATATCAAATAAAAGTTTCTGCACAGCATAAAACAAATCAACAGA
GTAAAGACATGACGTATGGAATGAGAGAAAATATTGACATCTGACAAAGG
GTTAATATCCAAAATATATAAGTAATTCACACAACCTCAGTAACAAAAGCC
AAATAACCTGACTTTTTTTTTTAAATGGGCAAAGTACCTGAATAGGTATTC
CTCAAAGAAGACATACAAATGGCCAAGAGATGTATGAAAAGCTGCTTAA
CATAACTAATCATCAGAGAAATACACAAATCAAAACAAGATATCATCTCA
CACCTGTTAGAATGGCTATTATTAATAAATGAGATAAGTGTGGCCAGGT
GTGGAGGAAAGGAAACCCTTGTACATTATTCATAGGAATGTAAATTAGTA
CAGCCATTATGGAGAACAGTATGGAGATTCCTAACAAAATTAAAAATAG
AATTACCATATGACCCAGCAATTCCACTTCAAGGAATACATTCAAATACT
ATCAGTATCTCAATAAGATACTTGCACTCCTATGTTTCGTTGCAGCGTTAT
TCACCATAGCCAAGATACAGAAACAAGTTAAATGTCCATCAACAGATAAA
TGGATAAAGAAAATCAGGTACATATATATACAAATGGAATATTATTCAG
CAAAATCCTGACATCTGAGATAACCTGGATAAACCTGGAGGACATTATGC
TAAGTAAAATCAAAGCCTGACACAGAAAGACAAATACCACATAATCTCAC
TTACATATGAAATATGAAAATGTTAATTTTATGGAAACAGAGTAGAATGG
TAGTTGCCAGAGCCTGAGAGTAGAGAAAATGAGATGCTTGTCAAATCAA
TCATCACATTGAATATATATAATCTATTTGTCAATTAAATATTTTAAGAA
TAAAAAATACCTGGCACCAAAAAAAGAATGCAAAATGTCTCAACAATGTT

ATATGTATTGCATTTTG. AGTGATAATAATTTGAATATTAGGTTAAATAA
AATATATTTGAAAAATTAACCTTCACCTATTTCTTTCCATTTTGTTAACA
TAGGTACAAAAAAATTAATAATTACCTATGTGGCTCATGTAGGTGGCTC
ACATTATACTTTGATGACACTATAACAGGCTGGTGACCATATATCTCTTAG
ACTAGTCTAAGTGATTTAACAGTGGTTCCAGAAAGATCCAGGTTTAACAC
CAATGAAAGGGCCAGCTGGCTTAGCCCAGCTTGTGTGGGAAATGTTGGGG
AGTGGTTTAAGACAGGGAAAAGCAAACTTTTGATGCTATTGACTTTTTG
AAAAATCTTTTGTGGCTGAAAAACCAAACATTATT

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GCTCGAGTGTGTCTCTAAAGCCTTTCCCCCATTTGGCTCCACTATACGCAC
TCTCCTGGTTTCTCCTCCCCTCTAGCCGCTGTCTTTGGTCTCCTTTCTGATT
TTGCTGCGTCTCTGTCCCCTGAATGATTGCTTCTCCACTACGGGGTGAT
TTTGCTCCCAGGGGACATTTGGCAATATCTGGAGAGGTCTATGGTTGTG
TTTGAGGGTGTGTGCTACTGCCATCTAGTGGGGAGAGGCTAAAGATGCTGT
TAATGCCCAGGACAGTCCCCATAACACAGAATTATTAGCTCAAAATATC
CATGGTGCCAAGATCAAGAAACCCTGCTCAAATATTAGCATGTGCTGAAG
GCCCTTCTCTTTCTTTAGCAATATCTGCCTCCTTAGGGATCTTTTCTAG
TCTCAGTGGTTTAACATTTAAAATCCCAAATTAGGCAATAAATTGGGCCC
CAAACCTTCGTTAGTATAAAATGTAGAAGTGTGTTATTAGAAGGCTAATAA
AATGACCTGGTGAGCATCTGCAGCTAGCCTCTGAGCAATTCTGGGGACCA
CGTGCAAGATAAATCCATCTGTTCCCTCTCTGTAATGTGGCGCTACCTTG
TGGCCGATTTTCTCCTCGGGTTAAATATCTCTGGGGATGCAACTTGTCGTG
GTTAATGGCTGTGTGAGGCCAGCGCGTGGTGATAAAGGAATCAATCAAGA
CAATATTGAATTTAGAAAGGCAGATTTATTAGAGAAAAGGAGAGATACG
TTGCAAGGGGAGCAATGGGCAATACAGCAGAGGGAAGGCTGTCTGCAAAGA
GGCAAGGGCTACGTATGACGTAGGGCTGCTTAGGCTGAATGCTTGCAGAC
AAGATGCTTGCGTGCAGGTGGGCTGTGAGCTGAGTGCTTGGGTGCTAGTG
AGCCATTGGCAGCTGACCCATTTTCTTGGAAACATTCGCTCCCTGCAAGCA
TTTTAATGTTAAACCGCCAGGTGAGTTTGAATTTTCTTTTTTCTTTTTT
TTTTTTTTTTTTTGCCTTTAGTAGGACCTGCCGTTGTGAGACTATCTGAGG
TAAATTAGACACCCTCCTGGTTTAAGTCACCGCTCCAGTGACTAGGCAGG
GAGCTCTTCCTTGAAGAGGGTGTGGGCAGTGGGTACTTTGCATGTTGTCC
ACACCAGGCGAGCTGCTGCTTCAGGGCCTTTGCATTTGCTCTTTTCTTTG
CCCAAATGCACTTCTCTCACTGTTTACATGATTTTTCTCCCTCTTTTCC
TTTTAGTCTTTGCTTAAATATCACCTTCTAGGGAGGCCTTCCACACCAC
CTCTTCAAGATTTGAGGGTATGCACCCCCACCCCTAGCCTTCTTATCCCT
CTCCACTGCTTTCTTCTCAAAGCACTTGTTACGTTCAAATAAAATAGATT
AGTTACTTTATAGTTCTAATTTTACTATTTTGTGTTACTTCATCAATAC
CCATGTAATCTCTGGAAGGAACGTTTCTTTTTGTAGTGTATTTCTAGCAC
CTAGAACAGTACTTGGCACATGGCAGGTGTTCAAAGTATTTGTTGATTA
TTTTCTCAAAGGGCATGGAGTCTTAGAAGTTTGAGAACACAGTTCTAAGC
ACAGCTGTTTAGAGACTATGGATGATGCTAATGGCTGTATTCCCAGTAGG
TGGGGCAATTCTCAAATTGACCTGGAATCCTTGAGATCTGGGGACAGTCA
CCAAGCACTGGGCTCTGTGGGGAGAGATGTGCTGGTTTTTAGAGAGGAGA
ATAGCATCCTGGGGGACTTGGCCCCAGGGCTTTCCTGTCCCAATCTCTTC
CCAAGTGAAGTCCCAGAGGCAGGAGGCCTTGTCTGTAGCTGGTCAGTCCTG
TAACTGTTTCCCTCCCCTACACAGATGCAAAGAAGGCTGAGAAAAGCA
AGCTGTCAGGTGAGCAGGGGCCCTGACTCCTCCCCAGAAGGCACTCAGAA
CTTCCATAGGGCAACTGGAAAGAAGGTTCTACTTCTCACCAGGAGCTGT
TGCTGGGGGAAAAACCAGCCTCAGGCCCTACCCTGTGCTGAGAACCTGAA
TCCAGTATCAGGTTCTCCAACAACTTGGATCCAGCTGACCCTCACAAGG
GGTCAGATGCAACCTTGTAGCATATGGAAAATGGCAGCAAGGTCCTTGTG
TGGACTATGCCTAGAATCTAAATTAAGACAAGGCCTCAGAGGGGCTAAGT
GACATCTGTCTCCAAAGTTTACAGCTAGTGTGTGACTAAATCTTGATTCT
CACCTCTCAGGTTTACCATAATCCCAAAAAGGTTGAAACAAGAAAAG
TTATCTTTGGGCAATTACCTCTTTCTGTTCTTCTGCTTTACCTACTAATGT
TCTAGGCTCACCTCTGGTCTGCAATCTCACTGAACTGACAGATCCCTCA
TGGCCTAAAGGGTTTTCACTGGGTTGACTAGGCTCTCCATTGCCTGT
CCTACTGTCTAAGGCACCTCCTGGGTAGGGTGCCAGCGTCATTCTGATG
CTGCCTGACTTTCCTTCCAGCTACTTTTGAAACTTGGTATCCATGGCAGA

[illegible]

TCCCAGCGTGATTTGGC .TACTTTGGGAGGCTGAAGCGGGTGGATTG
TGAGCTCAGGAATTCAAGACCAGCCTGGTCAACACGGTGAAACCCTATCT
CTACTAAAATACAAAAAATTAGCCGGGCATGGTGGCAGGCGCCTATAATC
CCAGCTACTTGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCAGGAGGCG
GATGTTGTCATGAGCTGAGATCGCGCCATTGCACTCAAGCCAGGGCAAGA
ATAACAAGACTCTGTCTCACAACAAACAAGCGAACATACGAAACAAACGT
AACATCCAACTAGCAGGTACATGCCGTGCCAGTCATGACCCATGGTCAT
AAGATGTCTACAGCTCAGGAAGCAGCTGCACAATGCCTGCATAGACAAAC
TCTTATGAAAGCAGAATGTCCTGATGTCTCCATAACACATAACAGTGTAT
GCTTTTATTATGGTCATACTCTAGCTGTGATGTACCTACGCTCTAATATG
CCAACGATAGTTTTCTTTAAATCATCAACATAATAAATGTCATGCTGTCA
GTCCCCACATGTAGACATAACTTAGCTGGTACATGGATAAGAAACCTAT
ATTAGATAACCTTAGGCCAGGTGTGGTGGCTCATGCCTGTAATCCCAGCA
CTTTGGGGAGGCCGAAGCGGGTGGATCACGAGGTCAGGAGATCGAGACCA
CCCTGGCTAACACAGTGAAACCCCGTCTCTACTAAAAATACAAAAAAA
TTAACCGGGCATGGTGGCAGGCACCTGTGGTCCCAGCTACTCAGGAAGCT
GAGGCGGGAGAATGGCGTGAACCCAGGAGGCGGAGGTTGCAGTAAGCCGA
GATCACACCACTGCACTCCAGCCTGGGGGACAGAGCGCAAGATTTCTGTCT
CCCAACCCAAAANCNANNNNAAATTTGCACCCAAATCTGACTAATTCCA
GAGCCAATTCCAATTTAGAATCGTTATATCTCCCTGGTGAAGTGAAGCTT
TTATCTTTAAGGAGACACACTCTTTATGTCTACCAATGCTTATTGECTTA
AAGTCCACTTTGTGAGATACAGCTGCTTTCTTTTAATTAGTTTTTGTGTG
GTATATCTCTTTCCATCCTTTTTCTTTTCAGCCTTCTCCATTCTTACATTT
TAGATATATTTCTTTTTCTTTTTTTTTTGAGAGAGAGTCTCACTCTCTC
GCCAGGCTGGAGTAGTGCAATGGCGCGATCTTAGCTCACTGCAACCTCC
ACCTCCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGG
ATTACAGGAGCCCACCACCAAGCCAGCTAATTTGTTGTATTTTGTAGAAG
AGATGAGGTTTCGCCATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCA
GGTCATCCACCCACCTCGGCTTTCCCAAAGTGTTGGTATTACAGGCGCGA
GCCACCATGCCCAGCTGATTTTAGCTGTATCTCAAAAACAGCATGGGTTC
TGTTTGCTTTCCTTATTCAGCTTTATAATGTAAATCATTTACATCAAACA
TCTAATACACCATGGACTGTAAAACACAGCCATATTTTATGTATGAATTA
AAAAAAAACACCACCAATTAGTTCCTGAGACACACACCTTAACAATAT
CTCTGTGATGTGCATAAATCAATCACATCAGTTTCTCTGCACCTCAAAAT
TTCTTTCCTCAATTCTCAGAGATATGGCAATTTCTCTGGTTTTACATTCC
CAGAAGCAAAGAAAAAGTACACAGCTTCTTCAAGTCATGAGTAGCTTCTT
TTTTATAGCTCTTGGTGTGTTGCAAAAAGATTGGAATTGCTTCACTAATA
CTAAATTTTCATTCTGCTGCTCTGTTTCTATGACAAGTCAGAGGGCATCT
TTTTGAAGACATTCTAAACAGCAATTAAGTCAAAACATGTAATGACAAT
GACACACAAAACCTCAACTGATGACCAAATGAAGAGTTCCAGCCAAGTTGA
CACAAGCTGGCTGACAGAGCTTGTAAACACACAGCTTGGCATATGCCTC
GCCATTTTCAGAGATGTAAAATAGGAATAAATGTTTTCCCTTAAATCAAT
GAAATAGAGCATTGAGACTGAAAATCTACGACAGTTATAGTGTCTTCTAT
TCATTATTCTCATTCTGTTTCTTCTCCCCCTTGCTTTCTTTTAGTTTGAA
TATTTTCTATCATTTCTTTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCT
TATTTTCTATTTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCT
CCTTAATTTATTTAAAAAATAATGTTAATGAGTAGCTTTATTTTCTTCT
CATCTAATTTAAGGCCACAGAACACCTTCACTTACCTCAATCCTCTCCC
AACTTACATGCTTTTAAATGTCATATATGTTAATACCGTATACTTTTAAAA
CTTTCTAAATAGCATTATTTTATAGCATGAGTGTTCATTTACATTTTGTG
CATATATTTAGAATTTTCTTTGCTCTTCTGTTTCTTCTTCTTCTTCTTCT
CCCCTCTGGGATCATTTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCT
ACTATTCAATACAGTAGCCACTAGCCATGTGTAGCTATTGAAGTTTAAAC
TAAGTAAAATTGAGTAATATTA AAAACTCAGTTCCTTCATCTCACTAGCC
ACATTTCAAGTGCTCAGCAGCCACATGTGACTAATGACTACTGTACAGCA
AACATATAGAACATTTCCATCATGGCAAAGAGCTCTATTGATAGTGTTCA
TCCAGAGTTTCTGTTCCAGGACCAAACCTGAGGGTTGGGCTGCTATTTCTC
ATGGCCCAATAACAAGATGCAGATGAGCTGGGGAGGAAGAGAGTTTTTAT
TTCTGCAACCAGTTACAGGGAGAAGGCTGGAAATCATCACCAGGCCAAC
TCAAAATTATGACGTTTTCCAGAGCTTATATACCTTCTAAGCTATATGTC

FIG. 4 (35 of 61)

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TACGTGTAAGTGTGCAT1 CACCTGAAGACGTAAGTGATTAACCTTCTTT1A
ATCTGTAAGTCTGAGTCCGGAAGATCTTCCCCTGGAGCCTCAGTA
AATTTACTTAATCTAAATGGGTCCAGGTGCTGGGGTAATTACCCTTATCT
TGTCCCCTGCTAAATCATGGAGGTTTGGGGAATTCCTTTAGAGCACCAT
TAACCTGTTTGTGAAGGCCTGGGAATTTCTCCAAACCCCCATTAAACC
TGTTTAATCCCAAATTGGTTCCGTTAAAAATTCCTCCTTAATTTGTCCA
ATTTTAAAGGCCCAAAAAAGGCTGGGGCAAACCTCCTGAATGGCCTTTGTT
ACATTCCAACCTTTGTTTAAAAACACCGGTTTTTAATATTTAACTTAACC
ATTTAATCTCTACTGAAACACTTGTATATAAATCTGCATTAATGAGAAC
TGGCCTGCGCCATATCTCCTTCTCAGAATATCTTAGGGTTGTGATCCCCT
GTGTGAAGAGAATATATCTCTGGAGATCTCAATCTCTCTACCCCAAAAAA
AATCTCACTCGGAGAAACTCAGACTCTTATCTCCACAGCGCTATCTCTC
TCCTCTCC

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GCTTGTCTAAGATGGTGTCTCCTTGTGCTGTGCCTGCTTTCATCCTGGGA
TCTCCCTTCACCATCAGGATTGCCTTCACCTCATTCCAGTCTTGGATCTT
TCTTCTTGTTTCTTGAGTATTTTTTTTTTTTTTTTTTGTGCTGCATTCCCTTCA
GTGGCCTCTTGGGAAAAGATGTGTAGGGAGAAAAATTTTCTTTAGAAACT
TGCATATCTGACAATATATTTATCCTATCCTGACATTTGGTAGATAGTTC
AGCTGGGTACAGAATTCTAATTAATTTTCTTCTGATTTATAAGACATT
GCTCCATTTTCTTCTGGCTTCCAATATTGCTGCTGAGAAGTCTGACACCA
TTCAAATGCCTGATTTTTTCCATGTGATTGTTGTTTTCTGTCTGGAGTGT
TGTAGGATTGCCTCTTTATCTACAGTGTCTGAAATTTTCATGACGTAGGT
CTTTCTTCATTCAATTATGGTAGACACTCAGTGGGCCATTTAATCGGGAAA
AACATGTGTTCTTCAAGTTCTACAACTTTATTACTTCCTTTTTCTTG TG
TCTTTCTCTGGTCTGTTTTTCAGCCCCGAGTCTCTTAGATCTGTCCTCTAA
TATTCCTATTGACTTTACTTCATTTTCTAAGTCTTTATCCTTTTGCTTTA
CTTTCCGAGAGACCTGCTTAACCTTATCTCCCAACTCTTTTATTGAATTT
CATTTCTTTTACTATATATTTTTTACTTTGAATACACCTCTCTCTTCCTC
ACATTTTCCCCCATAGTATTTTGTCTTCAATTGACAGTTCCTACTATCTTA
TTACTCTGGAGATATTAATAATAGTTTTTAAATTTTATTATTTTATT
TTCAAACAGTGTCTTACTCTGTCACTCAGGCTGGAGTGCAGTGGTGTGA
TCATGGATCACTGCAGCCTTGATCTCTGAGCTCAAGCTATCCTCCTGCTT
CAGCCTCCCAAGTAGCTGGAACCACAGGCATGTGTCACCATAACCAGCTA
ATTTTTTTGTTTTTGAGGTGGAGTCTCACTCTGTAGCCCGGTCTGGAGTG
CAGTGGTGCAATCTGGGCTCACAGCAACCTCTGCCTCCTGGGTCTGGTT
CAAGCAATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTACAGAAACA
CACTACCATGCCCAGCTAATTTTTGTATTTTTGTAGAGACAGGTTTCACC
ATGTTGGGCAGCCTGGGTCTGAACTCCTGACTTGTGATCTGCCCCTTGG
GCTCCCCAAAGTGTTGGGATTACAGGCGTGAGCCACTGCACCCGGCCACT
AATTTTTAAATTGTTAATAAAGACGAGGTCTTGCTATGTTGCCCAGTATG
GTCTTGAACCTCGTGGGCTTAAGTAATCTTCTGCCTCAGCCTCCCAAAGTG
TTGGGATTACAGGTGTGAGCCACTGAATCTGACATTTTTTAAAAGTTTTT
TTCTCTTTACCAAGTCTTTTTTCCCCTTTCTGCTTTTTTGGGTGTTTTA
TTTTGATCTCTATCTTGCTAGAACTTTCTGGAGACGTTTAGTAATACTA
GATTTTTGAGAGTGGGCAACTGGAAAGCTGATTGGAAACTCTGAATACAT
GGGTGAGGCTTGTGGCTGTGAGTGTGATTGCTTGATGTCCTGGCAAGGC
CAATGGGTTTGGGACCCCTACTATTAGTATAGGCCTGATTCCCTGGGAAA
GGCTCTTTTGATCTCCTGCCTGGAGGATAAAGGCCTGGCTACCAGCCTTC
TGTGTGAATGTGAGGGAGAAGGGCTGGAGTATTCAACATCATGCTGAAT
CCTTTCAATGATCATCTTGTTTTTTAGTAATCTCCTACCTTAACTCTCTGT
CTTCTGCTAGTATGGGAAAGATGACCTGAAATCTAACCATTTATTTTTC
CCCCATTAATATCATTTTATGATTATTCAGAAGTTAAATAATTGTCATGC
TGTCCTCCAAAAAGACTGAATCAACTAGCAACAAATAAGAATTTTCTCAC
AGCTCTGCCAGCATTTTAAAGAATAGCTTTATTGAGCCCAGGAGGTCAA
GGCTGCAGTGAGCTGTGATTACACCACTCTACCCAGCCTGGGTGACAGA
GCAAAACCTGTCTCAAAAAAGAAATTTAAGGAACAGCTTTATTGTTGTA
AAATAGACATACAATAAACAGAGCACATATTTAAATTGTGCAACTTATAC
TTTGATATAACCCTGTGAAACATCACCACAATCAAGATAGTGAATATAT
TTATCACCTCCTGATACAGTTTAGCTCTGTGTCCCCACCTAAGTCTCATG

TTGAATTGTAATCCCCAATGCTGGGGGAGGGGCTTTGTGGGAGGTGAT1G
AATTGTGGGGGTGCACTTCCCCCTTGCTGTTCTTGAGATAGTGAATGAGC
TCTCATGAGCTCCCCTTCACTCACTCTCTTTCCTGCTGCCATGTGAGGAT
GTGCTTGCCTCTTCTTTGCCCTTCTGCCATGATGTGTTTCTGAGTCCTC
CCTAACCATGCCTCCTGTACAGCTTGCAGAACTGTGAGTCAGTTAAATCT
CTTTTCTTCATAAATTACCCAGTCTCAGGTGGCTCTTTATAGCAGTGTGA
AAAGGAACTAATATACCTCCTAAGTTACCTCAAGCTTCTTCTTAATTCCT
TCTCCTCCCTTCCTTCATTGCCAAGCAAACAACCACTGTTTTCTGTCAC
TATAGATTAGTTTACATTTTGTGGGTTTTTTTTTTTTTTTGAGACAAGGTC
TCACTCTGTTGCCCAGGATGGAGTGCAGTGGTGCGATCATAGCTCATTGC
AGCCTTGAACCTCTAGTTTCAAGTGGTCTCCCACTTCAGCCTCCTGAGT
ACCTGGGACTACAGGGGTACACCACCACAACCTGGCTTAAAAAATTTTTTA
AATAAAAAATGGGGTCTTGTTATGTTTCTCAGGCTGGTCTCGAACTCCTCG
CCTCAAGCAGCCCTCCCTCCTTGCCCTCCCAAATTGTTGGGATTACAGGC
ATGAGTCATGACTCCTGGCCTAGTTTACATTTTCTAGAGTTTGTATAAA
TGGAACATACAGAATGTATTTTTTTCGGGAGTGGGGGAGTGTTTCTATT
TCTTTCTTTCTTTTTTCTTTTTTTTTTTTTTTTTTTTGAGACGGAGTCTCG
CTCTGTCTGTTGCCCAGGCTGGAGTGCAGTGGTGCGATCTCGGCTCACCG
CAAGCTCCACCTCCCGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCTGAG
TAGCTGGGACTACAGGCGCCCGCCACCACACCTGGCTAATTTTTTTTGTA
TTTTTGGTAGAGACGGGGTTTCAACATGTTAGCCAGGATGGTCTCGATCT
CCTGACCTCGTGATCTGCCCCGCTTCGGCCTCCCTAAGTGCTGGGATTACA
GGCGTGAGCCACCGTGCCCGGCCCAAGTGTTTCTATTTCTTAACCAGCTT
TCATGCAATCTTTTTTTTATTTTACCATCTCTGTGATCCCACTCCCAAAGG
TACTAGATGTCGATTGGTCTTAGGATCAGCTACCATTGCCCCAAGTCT
TTCCAGCCTTCCAAAAATTTTTTCTTTTTTTCTTAAAGATACTCCTGTG
TGAGGCTCAGAACTCTTGAATTGCTACTGCAAAATATGAACTCGGTGATGT
GAATGCCAGGGAATTGCCTGATTGATCAAAGAAATGTATCCCCTTCTCCC
TCACTCTTGCTGTCTTCTCATTTGTTTTCCCCATCCTTGTGGATTCTGTGA
ATTTAAATATCCCTTTAATGTTATAATATTTAATGGCGTTTGGCGAAAA
GTACAGAATTAGGTGCAAGAGTGCATAGCTGTTATTTTTTTTTTTGGCCTC
TGAGACTGTTTATATATGCAAGTTATTTAACAGAAAGTTCTGCAGTGACC
TGAGATGTCAGGGGGGTCTGATAGAGTACGTTTGAAGGCAGTTACTGGAA
AAAAATAATGCCATTTCTGGTTTGTACTTCGGTAAGTTCAGATGACCCAA
TATATTGTTTACATGTGGCATTGAGTAAAAAAGTAGCTTCCCCTCCCTTT
CTTCTTCCCTTTTCTCCTTTCCTGCTTCTATAAAGCATCTGCTTTGGGAAA
CTTCTTAGGAGGAGAGCTTGCCAGCCCGTGGGTAATGGAGAGGTCTTGCA
GAGATAAAAGAGATGCTCCCACTCAATGCAGGATGGTGTGGAGGTAAATG
GGGATACGTCTGGCATCACTCAGGAATGGGCCTTCCTGGCAGGGAAGAGA
AGGGAGGGGAAAGAGGAAGGGAGTCAAAGATGAATTGCTGAATACGGGGA
TTCCAGGGCCTGGAGCCAGGAAGAGAACTTTGGGAGGTGTGAACCTGGAG
GGCATCAGCTGATGAGGAGCAGCCTGAAGTCCGGGGAGGACCTGTTTTTG
GTGGCCAGGAAGAAAGTGCTTCCACACACAGGGAGGCCACAAGGCTGAT
GGGCTGGGGGTTGGAAGGACAGCCCTAGGACAGGCTTGGGAAGCAGGCTC
AGGTAGGGACTGCGAGGTTCTTGTTGAGTCTTTTTTCACTCCTGGTCTTAG
AAAATAGAATCCAAGGCCTCTTGAGAGTGGAAGGTGGGTGGGAGGAGGG
CAGATGGGGCTTAGGCCCAGGACACCCGTAGAGCTACTGCCAGCTGTCT
CTCAGGGACTCTGCTGAGGTCACTCCAAGGATCATTCTTAGCCTTGCTAG
ACAGTACTGACAGAGGGAACCGTAGTATCGCACCCACTTCCTTCTCTTTC
AATGAAAGTTTAAAGGTCACCATTTCTCTGGCAAAGGAAGTTCCACAAA
TATTCCATTTCCGGTCTTAGAAACAGCAAGGTATCAAGCAATTGCAAAC
TCCTGTGCTGGGGAATTCCAAGGAAGTAGGGGCAGAGTTCTGGTGGAGA
CAAAGTGAATTCCGAGTGATTAGTCAGTAGCAGTAGCAGTAGCAGTAGCA
GTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGTAGCAGC
AGCAGAACCAGAATTTCCCCGCACGTGTCTCAGGCTCTCATTTGCCAACT
CAGTCTCTAAGTATTTTTATTGGCAGGAAAAATAAAATAGCTATGAGTGA
AATAATTCATTAGACCTGAGCCTCCATCAATTTTGTGTTTAAAGGCCTGA
CTCTCTTTACCTTTCCCTGGGATGGAAGATGCAAATGTTCTGATGTCAC
TGTCAAAAAAGAAGAACCAGTGGGTATATTGTATGCTTGAGTTCCAGCCA
TTTGTCACAATAGATAGAGATGACTGCCATGTGTGTAGACTTTCTATAGA

CTGTGTGCTAAACCCGAUCTGCCACTTCCAAGGAGTAGATGAGGAATG.C
CATGGTTCTGGGGAGCCCTACCCCAATTTGGGGCAGACATTCCAAAGCTC
ATTTTCTGTGGAGGGGGTTGATGGTTAAAGGACGGCCTGGGAGTAACTCG
TCTGTACTAGGGCCAGGAGAGTTACATGCTGCTTCCCATGTTATTCATC
ATTCCCCCATGTGAATAGCTATGGCGTGAGGTCCAAGGTTAGGGCCTTTC
TACCATAAATGGGGGAATAAAATTTCCCTACCAGCCTGAGAAGTTTCTGT
TATAAAGAGGCTTTTTTTTTTTCGCGGGGGTGGGGGAGCAAGCCGACTAATGT
GTTATTTCCATACGGTTTGTTTTAAATGTAGATGTCATATGCAGGAGAG
GTGGTGTAGTGAGTCACAACGGGATTAGAAGGACCAGTCCGAAAGCAGA
AGAGGGTCAAGTTCAGGGCACTGAGGACTACTGCATTCAGTGGCGTGAAA
GGCAGATGGCTGAACAGGAGGGGGACATTACATTGCTTGTCTCCTTGAG
CCTCGATTTCTCATCTAAAAAGAGGGTCATTTATTACAGAACATTTAT
TAACTTGTGCCAGGCACCGTGCCAGGAGCTGGACTAAAAATTAAATCCA
CCCCTGTGAGCTGCTCTGAAGGCTAAATATGAAGTATGTAAAAGTAACC
AAGTGCTGTACACATGCAGCTATTCAATGACTGTGTGGGCATTGCGGCAG
ATTTTAATTTTCTTTTTTATTCTTTCTCTTTAGTGAGAGGTGTTGGTTG
TTATTATTGTCGTCGCTGTAAGTGTCTATTTCACTTGCTTTTTTGTGGCC
TCCAGCCCATTCCAGGGCTGTCTAAGACACTTCTTATCACCTAAATA
ACCGGGGAGGCAAAGCGCTTTCTTAAGAGATGGATCCAGAAGAACAATGC
TGGTTTTCTGTAGAAAAGGGGCTGTGGGAAGTAGAGATAAGAAGGGAAT
TGGCCAAGATGAATGTACAGAGCCTTATTTTTTTTTTATAACACAGCAAG
ATTAGATACAAAACAGGACAATAGCATCATCTGTTTTTATAACTGGAAAG
GACCTCACTTTACAGGTGGGAAGAATAGAGTGGAGAAGTGAAGAGAATG
GTCACAGAGTCAATCAGCATGTCTGCGTCAAAGCTGGGATTCCCAATTCA
GGGCTCTTACTACAGTGACGTATGGCTAATATTTTGGCATTGTTTCGGGG
AAAAGCTGAAGCCCTGATGGTGTACGTCACTCTTGAGATAGTCTGTAGTC
CAGCAGGGAGGAAAGCAAGGAAGGGAGGTGGAGGCAGCATTTTTGGGTGT
AACATTTCTGTTCTTGTTTTGTGGCCAAATCATAGTGTGATTGGGACAAGC
CACTGCCTTTCTCTGAGCCTCCACTTTCTTTTTCTTCTTAAGAGGGAGGG
AATAGTAGAGTAAAAGTAGTCATTTTATCAAACACCTGCTATTTTGGAGC
CATATTGCAAGTGGGTGGGGGTGAACACTTGGCTTTATTACCCATAGG
ATTAAATCCAACCTCGATACTGTGGCATTCCCAAACCTCCAGTCTAATCTT
CTTCTCCATCAGCCATGCCCCACGACACCCTGGTCATATCTGATGTTGCC
CCTTGCACTTGCCCCCTCCTTATCTTTGCTTTCTGACCTACCATATGGCT
ATTGGTTGAAATTCTCATTTTCCAGGGCCTTGCTTAAATATCATCTCATC
CATTAAAACTTTCTTGAACCTCCCCTTGCCCTGTTCCCTCCCTAATGTCTC
AAGCCAGAATTTATTTCTTTTGTGGCCAAGGGACTGGGTTTGTGACCTC
TCTCACGAGACTTAATATTGAGACCAAACGTCTTTAGACCTCACCAGCCA
GAGAGATGAGCATCTATGGAATGCAGGCTTTTGCCCTGGACTTGCTGATGC
AGGGCCTCTGCCTTCTCCAGGGCCTCTCCTGCTGTTTTAGGAATTTCCC
TCATGGCACAGTCCATGAGCTCAGGGTCAAGTTCATACATGTTTTTACTT
CTTCTACTCTGCAAATGGTCTTCTTGAACCTCTGAGGGTCTTAAAGCTGCT
CTGCAGTTTGTGGGGTGAGTAGAAAGGGGCTTCAAAGTTGTGCTGTTG
TTTCCCACCCCAATAGCATGAAACACAAAGATGCTTACAAATAGCTGCCT
TGCTTTCTAGTCCCAACTTCTCTCTCCTGAGGCTTTAAACAAGTCCCCT
AGGTTGAGCTGGACTGGAGTTGTATCCTATCTTCATTATCTGTCTACTCT
CTTTCTGCTCTCTAGAGAAGATATTATATATGTGTGTATGTATGTGTAAA
TATAAATATCCATATATAGAACATATATTGTTATATTTACATATACATA
CATAACATATGCATGTATTCATATATACATATGTAGTATCAAAGTTGGAA
TTAAACTGTATATTTTGTAAATTTGCTTTTATTTGCATCTATCACTGTAAA
ATGAATATTTATCCATACCGTAAGATATTCTTCAATGTATTTTTTTTTT
TTTGAAACAGGGTCTTGCTTTGTTGCCAGGCTGGAGTGCAATGACCCGA
TCTTGGGTCACTGCAGCCTTGACCTCCCCGGCTCAAGTGATCTTCCCACC
TTAGCCCTCTGAGTAGCTGGGACTAAAGGTGTGTGCCTCCACACCCAGCT
TTTTAATTTTTTTTTGTATTTTTTTTTTAAAGACAGGGTTTTGCCACATTG
CCCAAGCTGGTCTTGAGCTCCTGGGTCCAAGCAATCCTCCCACCTTTGGCC
TCCCAAAGTGCTAAGATTACAAGCATGAGCCACCACACCTGGCCTCAATG
TAATTTTTAATGGCTGTATAGTATTCATCATGTGGTTGTACCCAAAATT
ATTTAACCAGTCCCAGTTTATTTCAATTTTTTTTTTACTATTTTGAATAA
TGTTTTAGTAAATACCCACAAAATATGTACAATGGCTGGGCTTAGTGGCT

FIG. 4 (38 f 61)

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CACCCCTGTAATCCCAA₁ACTTTGGGAGTCTGAGGCAGGTGGGTCA₂CCTG
AGGTGAGGAGTTGAGACCATCTTGGTTAACATGGTGAAACCCCGTCTCT
ACCAAAAATACAAAATTAGCCGGGTGTGGTGGCACACACCTGTAATCGC
AGCTACTTGGGAGGCTGAAGTAGGAAAATCACTTGAACCTAGGAGGCGGA
GGTTGCAGTGAGCCGAGATCACACTACTGTACTCCAGCATGGGCAACAGT
GAGACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAGTACAATTTGTTG
TACCTCCCTGATTATTTCTTTTAAGTAGAATTTTCTTATAATTTTTTTTA
TAAGTAAAATTTTGAATCAAGGGAGAAGCACCTGGAGTCCTTCAGATACC
TATTGCCAACTGAACTTTTCTGTTCCAGGTTTACTACATTCAGCCTGAC
TCAGGGTTTGGGGAGTAGAGGAGGGGGTGGAGGCAGAGGGCCTCTCCCTG
TCCCCACAGACCTCCCTTGGTGAGGTCCAAGTCTGGACAGGTGGAGTGTG
GCATTGCACCGTCAGGTCCTGCTTCCTGTAATTCCTTAAATCCATCCAG
TGGAGCCTCATTGTTCAAGTCTTTTTTTTTTTTTTTTTTTTAACTCCC
CTGAAGACGGAGTCTCACTCTGTGCCCCAGGCTGGAGTGCAGTGGCACGA
TCTTGACTCATTTCACCTCTGCCTCCCAGGTTCAAGTAATTCTCCTGCC
TCAGCCTCCTGAGTAGCTGGCACTACAGGCGTGTACCATCACGCCCGGCT
AATTTTTTTTTGTATTTTGTAGTAGAGACGGGGTTTCACCATGTTGGCCAG
GCTGGTCTCGAACTCCTAACCTTGTGATCTACCCGCCTCTGCCTCCCAA
GTGCTGGGCTTACAGGTGTGAGCCACCAGGCCTGGCCTCAAGTCTATTTT
TTAACTCCAGGAGGCCTGGTATTAGAGGGATTAGGGCTGGCAGAAGGGC
CTCAAAGCTTTCAGGCCTGGGGAATAGGCTGCAGCCTGGTTCAGGGTAA
CCCAAGTGATTTTGGTTCCAAAGGGACAGGAAAAAAGTGATTGATATGG
AAGTTGTCAAAGTGCAACTGTCAAGACATTAAAAAATGTAACCTTTTAC
TAATATACAGTAGACTTGTGTTAAATATTTAACTGATTGTAAAAGGAAAA
AACCAGACGCAGTTTTCCCTACCATACTGTCAACACCTCAACACTGAG
TTCTTCTGTGACCTCTAGTCACCGAAATGCTTGGGGATTTCTCCCACCAC
TAGTCCTCCAGCAGCCGACACCAGTTGGGTGTCTAATTCACTCCAACAC
TATCTACCTGGAGTTAGCGTTAGATCCCACAGGTTGAGGGCTCAGTCTCA
CAAGACTGCCTCCCACTTCAGGTGCCAGTTACAAGTGGTAGGTTGTCACC
TATGCTTCTGACTGATGGCTATAAATCTGGGTTTGCTTCCCTCGGGTTCC
GTGAATTTGCTAGAGCAGCTCACAGAACTCAGGAAAACACTTAAGTTTAC
CAGTTTATTCTAAAAGATATTACAAAGGATACAGATGAACACCAGATGAA
GAGATGCGCAGAGCAAAGCATGTGAGAAGGGGTGTGGAGCTTCCATGCCC
CTCTGGGGCACCACCCTCCAGGAACCTTCATGTGTCCAGCTATCTGGGAG
CCCTTCCAAACCCTGTCTTTTTTGGGTTTTTAAGAGTGGCTTTATTACAT
ACACATGATTGACCGAACCATTGGCCATTGGTGACTGACACAACCTTCAG
CCCCCTCCACTCCCTCCAGTGGTTGGGGAGTGGGGCTAACAGTCTCAAGTC
TCCAATCCTGCCTTGGTCTTTCCTGTGACAAACCCCATCATGAAGCTACT
GCATTGGGGCTGCCAGCCAGCAGTCATCTATTAGCATGCAAAGACACTC
TTATTATTCCAGAGATTCCAAGGGTTTTTAAAGCTGTATGTCAGGAAAC
AGGAGATGAAGAACAAATATATATTTTACAACATCACACTCGTTGGGGGA
ATTGACAGGATAGCAAACCTGATTAAAGGAGGATAGGAGAGACTGAGATA
TATATTTCCATATATATATATAGAGAGAGAGAGATATTTCCATATATA
TATATAGATCTAGAGAGAGAGAGAGATAGAGAGAGAAGAGTCTTTCC

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ACACATTTGGGGGAGCAGTTCCGGAGGTACAGCCCGGACAGGAGATGTGA
GAAGATCGTGGTTANTGTTCCCTGGTCCAGAACCCTCCAAGTGGGCTT
AAGTAGGAAGGGTGGTGAGCGGCAGGTAAACACACGTCAAAGGCAGTCTT
CCTCTCTGAGGGAAAACACTTGTATAAGCATTGCAATCAATGGGCCTCTT
TAATTATGTGCCAGTGGCAAGAGCGGGTGCTGAACCCAGGGGCCTGCCTC
AATCCGGGGCCTTTGAGGCAGAATAAAGTGGTCTCAGGTTGTTGGCATTT
CCTTGCCCTTCCACCCGAAGCAGACACAAATCCTCTCTGGAGGCAAGTTC
CCCAATTCAGCCAGTACAACTCCCACAGACTAAGATCAATCATGTACAAG
CTCACAGACAAAGGTCACCAACACACAGAGCAATAAACAAATTCATGAG
TGACGTGAATGAGAATAAACAGAAACAATAACCACCAGCTGGGATGCTCT
AAGTCTTCAGCTGTTAGAATTCCTGAATATAGAATAAACTGCCACAATG
GCAACATGCATCTAGTACTTACTGTGTGCTGGGTTCTAAGAATTTTGCA
CATTGTGCCAGATACCGACTCAGCTTCACACTCACCTCCTACTGTGCC
TCTTAATTTGCACTAGATTAAAGGTAGAAAGGAAGAGGCAGCTATTCTG
TTCTTGGCTGTGCCTCTGGCAGCACATGCAAATGGGCAGTAACAGTGGC

FIG. 4 (39 of 61)

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AGTCACAGGTAAGTAGC TTCTCACAGTGGAGTTAAAGGCATGGGA
GAGACGAGCAAGGTTCCCTAAAGGGACAGTGGCCAGTAAATGACCAGGGGC
TACTGGAGTGGCTGCATGGCTCTGTGGAAGCTCAGAGGAGCCTTGGGTCC
TGCAGGTGCAGTAGCAGCTTTCTGTAGTTCTCTGATCTCTGGGTCCCACAA
TCTTCCCCGTTTTTGTCTCCTCCACTTCTAATTTTGTAACTGACTTCCCTG
TGTGTACTTCTCTCTCTGATTGAAATAGCCAGACTGGTTTCTGTTTCCTG
ATAAGACATTGTCTGGTACGAACACAGTAACTCATTTAATCCGATATCTC
TATGAAGGAGGTACAATAATTATTCCTATTTTACAGATGAGGAAACACAG
CAGAAAAATAAAGTCAATTGTCTAAGGTTGCACATTTAGTCAAGGGAAGG
GTTGATATAACATATAATTATTTAGAAAACATCTAAGGAAATAAAAGGCA
TAATTTAAAAATAAACTAGGCAGGTTTAAAAAAATGAAGTAATCTATAA
GTAAAAAAGTATAATTGTTGAAATACATATCTTAGTGGATGGGTAAATA
GCTGAAGAAATGATTAATGAACTGGAAGGTAGTTCTGAGGAAATCAGAAT
TCAGCATAGATAGAAAAAATGGGAATTTACAAAAGTACACAGGAATTATA
AAAGAGGTTAAATTATAGGGAGGGTAGAATGAGAATTAACATTGGTCTAA
CTGGAATTTTGAAGAAGAGAATAGAGAGAATGAACAAGGCAATATTTAA
AGAGGTGGCTGAGAATTTTTCAGAACCAACACAACTATGACTTTACCAG
TAGAGAAAACAATGTACACTGAGGAGGATAAATAAATACTATGAACAA
ATTGTAATAATAACTCAACAAAGACAAAGAGAAGATCTTAAATCAGC
AAAAAAGAAAGTCAGACTTAGAAAGAAATGACAATGGCAGACTACTCAA
CAACAACAATGGAAACCAAATTCAGTGAACAGTATTTTCAAATGCATA
TTTAATCTATCTTTGAAGAATAAGGGTGAAAAGGGTGAAAATTGCTGCCT
TATACAAAATATCAACATTAACAAAAAGTAATGAAGGTAATATAAAAATG
TTTTCAAATAAACAAACTGAGAGAGTTTACCACCAACAAGCATTCTTA
AATGGACTTTTAAATGCAGTTTTTAGGAAGAAGGAAAACAATTCCTAAGG
AAGGTCTGAGATGCAAAAAGGAATTATGAACAAAGAAATTGTTAAAATTA
TAGGTGAATTAAAAAAACTGCCTGCATAAATGATAATAATGACAATGATG
CTATTAATAATGAGTTGATAAGGATAAAGAAAAGGACAGAATTAAAATAC
TAGAAAACAAGCATGCTGGAAAGGATTCAGGAATTACTTGAAGGTAAAG
TTCTAGGGTCCTTCTATCCTTCTAGAGGGGAGTCAATATATTAATTTTTG
ACCGTCACTTACACAGTGAAAAACTTTAAGGATAACCATAAAAAAATAGA
AATAGAGAGTATAACTTCTGAAACAGTCAAGGGAAAAATATGGAATAAGA
AACTGACCAAAAAACATCTCAGTCAATCAAAAAAAAAAAAAAAAAAGAAA
GAAAAGGTTCCGAAGGAGAAAATCAAAGCATAGAAAAGCGGGACAAATA
GAAGTGGAAGAAGAAAAGGTAGAAGAAACAGGTCCAGAAATATCACTGAT
GCACTAAATCACCATTAAAAGATGAAAACAAATGAACAACATCAAAAAAT
TCTAGTGACTGTAGTAGTGCTGATCAGAATAGGCTCTAAGATAAGATGCA
TTATTGTGAGTCAACTTGTGATGATGAAAGGTTTAATTCACCAGAAAGAC
ACAATTATAAACTTGTAATCAAATAGTTTTATTTTATTTACTTTATTTAT
TTATTTTTTTTTGAGACAGGATCTTGTTCTGTTGCTCAGGCTGGAGTGCAG
TGGCTTGATCTCAGCTCACTGCAGCCTCCACCTCTTGAGGCTCAAGCTTT
CTTCCTGCCTTAGCCTCATGAGTAGCTGGGTCCACAGGCACACACCACCA
AGCCCTGCTAATTTTTTGATTTTTTTGTAGAGATGGGGTTTCACCATGTTA
CCAGGCTGGTCTCAAACCTCCTGGGCTCAAGCGATCTGCCCCCTCGGCTT
CCCAAAGTGTTGGGATTATAGGCGTGAGCCACGGTGCCTGGCCTCAAATA
ACTATTTAAGTGAAACAAACTAGTATGGCACTAATGAAAAATGTATAAA
TCCATAATCGCAGAGGGATTTCAACTTACTTCTTTTGATTATGTAAAGGT
CAAACAGACAAAAGACAATGACAAAACCTTAATGCAATGAACACTTTTGAT
TTAATGAACATATATTGGATATGTACCCAAGAATTAGAGAATACATACTA
GTTTTGAGTTTATGCAGAACATTTACAAAATTTAGTGGAAGCCTAAATT
ATAAAAAGTTGCTGTCACGTAGAATAACACACAAACCCCTGAGTCCGGAA
TTCAAAGCCCTCCACACTCTCCTCTACCTTTGCATCTTTATCCTCCACCA
CACTGCAGTGCATACTCTGGGCTACTACTCACTGTTCTTGATTCAAATTC
CATGTTCTGTGAGCTCAAATCATTCTCTCTGCCTGGAATAACTACTTCAT
ACATATTCTGCTATTGAATTCTTGCTTAGCACCCCATCTACTCCAAGAC
GATGTCCAGTTGGGGTTACTCCCTGTCCCATTTTCTTTGATTACACTTTT
TTTTTCTACTTCCATTATATTATTGATCACATCTGTGCCACAGTTTTTGA
CTTTGTGCTGCTTTTACTCTTTTCTAGACCCTGAGAGCTCCTGAAGGGT
TGGGTCAATTTCTTTTTTATTGCTCATTCCTCATGGCACAGTGAGTGCTT
AATAAATGGCTATTGACTGAAATTAACTGTATCTAAATGGACATATTCC

ACTTCTGGGCCATTTCATCTTTCTTTCTATTGGAACCAGGAGATGGGGAA
CCATAACAAAGGTAAGGTTGTGCCATGTGAAAGAACATGGAACCTTCCCC
TGAGGGCCAAAAAGAGCAGGGAAAGGTGCAAAGACAAAATCTTCCATTT
TTAAACAATGTAAGAATGTGGTCCACCTCATGCTCAGGTGGGACTTTATC
ATGACGTTATTTTTTGGGGACTTATAGCTGCATCATTACCCCATATACAT
TTACCTTTAGTGTAGGGAAGTGGAGACAGGAATTTTGTGTGATGCAGACTC
TTGCTAATGAGGCTAACACTTGGAGAATTTTATCATGCATTCAAGAAGC
TTGTTTTACATTTCTTCATTAATACTTTAGTTGGTGGTTTAGCTTTAGTT
GTAGGCTTATCAGATATTTGGAGATATCTTCATAAACGATGGCTTTGGTT
TTAGAAGAGTTATTCTGAAGCTACTATTTCTGGCAATAATCAAACAGCAT
GGCCATTTGTTTTGTAAGGCCTTTCCTAAATATGACGGTAAAATCTACG
TGTGGAAAAATGCTTATTCTTCTGTCTCTATAAATGTGAATCTAGTTTG
TCTTCAAAATGAAATCAAGTGATTAATAATGTAGTTTTCTAAGAAGATAAA
TGGAGCAAAGCACTCTGTGTTTCACAGTGTTGGAAATCACTCATCCCTCA
TAAACTGTCCCACTGATCCTGACTCACATGAATGAATTAAATAAGAG
TTAATAACATCAATTTACATTTTAAAGACACTTTCCCATGTTTTAGACT
ATTGGTTGGAAAAGCTGGTAGGTGTACAATTTGTGGAGAGTTGGCTGTTT
TTGTCTGTCGTTGTTTGACGTATTTCAAAGCCATATCTAATTTTGTTGCA
GAATGGTCTGAATTCTACAAAAATGTTGAGTTGTGTAGTGTGGAGAAGTA
CGGAGCCATTTACTGAAAGGCTGGGGGGAAATGACGAGACCCTGAGATAA
GGCAGTAGTGGTGCGAACAGAGTGGAAGGGAGGTAGTTGAGATATGTTCA
GAGTAGAATCAGAATGGACATAGTGAACAACCTGGATGCAGGTGGGGGCTG
AGGAAGCAAAGTTGAGGATAATTCTGAGACTTCTAGGTGATCCACTGAA
GTTACATTATTCAACACCACAAGGAACTAGGGGAATGAGAAGGCATACT
GGTTTGCTTTGGAGTGGAAGGGCAGTGATGTAAGAGGAGTTAATGAGTTA
AAGTTTGGATATGCCTGAACCTTCAATTTGATATGTGCATCTGATATACCC
TTGGGGTGACCCTCCAGGCAATGGTTGAACATGTGTATTTCTTAGTAACT
GATAGGCATCACAGACTCACATCAGTAAGGAAGCAACAGCAAACCTTGATT
GGACGATATACCTGGAACCTCAGTACCCTATGACTGGAGCAAGTCTCTGTC
AGTGAAATGAGGATAAGAAGAATCTTGACCTTGTGGAATATGTTGTTAGG
AATATATGTGATGAACAACATAGGATACTTCTACAGGGCTCCACATGTA
GTAAGGGCTTTATAAATGCTTGATAAATATTATTGTTGTAATTTATTTCC
AAAGTAAGATGCCACTGGAGGAATCTTTGGAACCCAAATTAATAACAAAT
AGGACTGGATGCAATGGCTCACACCTGTAATCCCAGCACTTTGGAAGGCC
AAGGCAGGAGGATCTCTTGAGCCCAGAAATTCAAGACCAGCCTGGGTGAC
ACAGGGAGACCTTGTATCTATGAAGAATTAATAAAAAATTAACCAGATGTG
GTGGTGCACGCCTATAGTCCCTGCTGCTTGAGAGGCTGAGGTGGGAGGAT
TGCTTGAGCCCATGAGGTTGAGGCTGCAGTGAGCCATAATTGTGCCACCA
CACTCCAGACTGGGTGACAGAGTGAGACCCTATCTCAAATAAATAAATAA
ATAAATAAATAAATAAGTACAAACCAGCAAACACTAATCCTTTCTAGAGA
TTATTGAACTCTGGAGGGCAGATCTGAATGGAGCCAGCAGAGGGACCTAT
GGAGATCAGCCTGGCCCTGGACAGCACCAGGCAATGGGGTTGCTAGAGAG
GTAATGGGGTTGAACAGGGTTTAAGCCATGAGGTCTCAAGAATCCGTGAA
GACTCAGACTAATTTTTTTTTTTTTTGCATGAGGATTAGGTGTTCCCTAGGA
ATTTCAATGAGAGCAGGGTTAATGAAGGAATGCAGGGTAGGAGAGCTGAG
GGAAGGCATCTGAGAGAGCCTGGCTTATGAATGGCTGCGTCAGTATGGCT
CACCTGCTTTCTTGTATCTACTTAGCAGATGATCCCAACCCAGGCCTCC
AGGGCCAAGGTCATTTCCACATAGTCATGGGCCCTTGAGGGCCTGGAGCA
GTGTAAGGAAGACAGAGTCTTAAGAAATTGCATTAACAGTCATGGTGCTT
GGCAAGTGTGTCATCCTATGCCAAGCCTGATCTGAAGGGGTGCATGCTC
ATAGGTAGCTGCTGCCCAAGATTACAGCAGCTTCTTCAATCCCAGATCCA
TGCTCTCCTATATTCAATTTTCCAGGGGTTCTGTCTTTCGACAGTGATG
AGATGCAGAATGACTTATTGAGTTATTCTCCTGATAGTTGCCAACTTTTC
CAAATGACAATGGGGCATGGAGCTTGAGAGTGGAATGAGGCCCTAGGGA
TAGCGTGCTTAGGAAAACACTCCCAGCCTGATGTAATTCTGGGGGTACAA
TGGCATTTTCATCATCAAGACTGATGTAAAGGGTGACTAGCAGTGAGTTG
GGGGTGACTCGCACTGGGGCTAGGTTTCTGATTCTGCCTAATCCAGACAG
AGCAGAAGCACTAGTGGGCTGGTAGAGGGCCTCCAGGGCCTCACTTAATG
TCCTGGAAAAACAGCTCCAGATTGTTGGTTTACGTTCTGAGGACAAGCTT
GGGTACTACAGGATAGAGAGAGTGGTGGGAGATGCCGTGGCCTGCCCTGC

TGATGCCTGCCCTGCCATTCTGCGTGTGATGTCTCTGGGGCATCTTGCC
TTCCCTGCCCAGACCTGTAGTTCAGCTGAGGGCATGTGGAGGCCAAATGG
CTTCTTAGAGTGTTACTTTCCTTGAACAGCTCTGCTGGGAGAACTGGAGG
AGCTAGCTAGTCACGGTAACTGCAGCAGTCAAAGGATCGTCCCGGTGGAG
GTGGGGTGGAAAGGTAGAGAAAGAGAACATATAGCGTTTTCTTGAGAT
GTGTGGGCATGTCATAGAGGAAATACCCAATTCTGAGCCTTGAGCCCTC
CAGGAAACCTTGGAATATTAGGTAGTCATCCCCAAGGAAGTCTAAGAAT
TCTGGTCTCACCCATCTCCTTTAATTCCCACAATGATCCTACATGATATT
AAGGAACACGGGCCAGTAACCCTCCAAGCAATGGATGTGGTGGTGAAGTT
TGACCTCATGATGGAGCGGAGGTTGGTTTGAAACCTAAGAATTTAATTTA
TTGTTTCAAACCTGTTCTCCACTCAGCGTTATTAAAGCATAACATAATTGAC
ACATAAAAATTGTATATGTCTACGGTGTACAATGTGATGTTTCGATCTAT
GTATACATTGTGAAATGATTACAACAAGCTAAATAACATAACCATTCATC
GTGTTTCAAAGGAATTAACTCAAGCACAAAAGAGAGGTGCTGTTGAAGA
GTAGGGCTGCTCTATCTAAGTAGTATGTCTGGGGTTGTCCTGGATCAGGG
TCCTTTTGTGCTAGTAATAAACCAGCCCTTCTGGGGCTGCTCEACTTTCC
CCACATTTTCTTCTGGAGCCTCCCTAAGAATTAGGACATGGCCACTTTCT
CTGCATAGGCTTCCTACTTCAACAAGGACAGGGCTTGTGCTGCCCCATGC
CACTTGAGTGTCCCTACAGCACAGAGCTGAGTGCACACTGGCTGAGTGAG
GAAATCCCCCAGATTAATCTTGGTTCTAAGCATCATGGCTGTATTTACA
CGTATATGAATTACAAATTACAGCATAGTCTGAATAAGGATTTTTGTGCTA
CAACTGGAATCCCAGATTATGCAAATTGGATAGTATAATATTGAAATTCC
TAGGACTTTTTATTAGTTTTTAAAAAATTATACAAGCTTAGAGTAAGAAAT
TAAACAGTGCAAAGAATTCACTGTGAAAAGTAAAATGCTCTGTCTCTGC
TGAGAGACAGATATTGCAGCCCAGATACTACTGGGGTCAATAGTTTTCTT
TAAGCATGCCATTTTGATGGTTTTATGGGACTTACAGCTCAAGAAGCTTGA
CACTAGGGTTGATCTCAGAAAATCATTGTTGCAGGTATTAGATATGACCG
TCTCATAAAGATACACACACAGACACAGCGATTGGAGATATTCACTGGGG
CTTATGGGCTGCTTGTCTTTCTGCTCTGTGCCTAAGTTGGGCTCAGAGT
AGCCTGGCATCGGCTGTGGGGAGAATGCTGGCATGGGGTTAGCAGGAGCC
CACTTAACATGTCCTAAGCCACCTGGAAGAGTCTTCAAGGAGACCAGAC
TCCAGAGGCCCTAAGGAAGGAAGGACTTTTGCCCGTTTTTAGGTATTCTA
GTCCCAGAGTTTAGGGAGGAATGGTTTGGCTTTGGGTCGTGTGCCCCTT
ACCGAGTGGGATGGGATGTGCCCATGAGCTGTTGAGCTGGCTCTTGAGGA
AGACAGCAAAAGCGGGAATAAGAGGTCAGGAAGCTGTGTGGTTGTAGGAA
ATCCCAGCAGAGGGCCTGGGGGTCAAAAGTGGTCATGGTAGTGACGGTGG
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CAATGCCAGTCACCTTCCTGTCCCATAAACTTTATTAAAGGTGCAGAA
TCCCATGGAAGCAGGTGGACACCATCTGCTTCCAGCCAGCCAGGGGAGCA

FIG. 4 (45 of 61)

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AGGTGTCCACTGTGCCTTTGTGGCAGGAAGTGGCTTCTCTACTCTCCCA
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AGGGCTTCATTCCATAGCATTCACTTACCTCCAGCTGTAGAGTGGGCTTA
TCATCTTTCAACACGCAGGACAGGTACAGATTCTTTTCCTTGAGGCCCAA
GGCCACAGGTATTTTGTCACTACTTTCTTCTCCTTGTAACAAAGGACATGG
AGAACACCACTGAAGAAAGAAGGGGGTCTTGTGGTTAGGGACACAGCAGT
GCAGGGTCACCCCAACCCCTAGGCCCATGAGTAGGATACATGTAATTTG
GTAGCCTCTGTGGGAACCCACAGTGAGGTTCTTGGCCTAAGACACAGGA
TAACTTGACTTCTCACAGACAATAGCAGGGTCATTTTGTGATTAGGGT
TTCCCTCAAAGGCCTGAGGGTTTCTCAGAGCCTCATAGCAGTAGGAACG
GAGAATGAAAGAGGGTCTACATTTTAAATGCTGAAGGAAGGAAGGAAGGA
AGCCATTGTGTCACTGGCTGGCAATGTGCCCATCCACAGGAGCGGAACAA
CTTGATCAATGTGGAAGGAAAGGAAAGAGGTGAGGCTGTACTTCTGCCAG
AAATCAGGCACCAGAACTGTTTCAGGAACAGAGAGTAGCCCATGGGAAGA
AACTGGGAGAGGAGAGGCTGAGCTGGGAAAGTGGCTCCAAAGAGAGACAC
TCATTTTGATCTTCTCAGTCACAGCAGTGTCAATTGGAAGGCCCTGGGA
TCACTCTTACTACCCGATTCCAAAGAAACAGGATTTTCTTGGCCTGGCTG
AGAGCAAATAGCTTCCCCCTTGAGTGAGGCTGTCTTCAAAGTCAGCAGC
CTTAGTTGCCCACACTCCTGTGCAGAGGCTTTGGCTACTGTGGCACGATG
CCAGGCAGATCACCACAGCTAATGATGGGTTACCGCACTTGAACTTTT
GCCCGTTACAGCGGAGAGATATAAGTTCTGTGGCGGTAAATTTCCC
TACAAGGAACACCTGGCATTGGGTGGGACGGATGTTGGGGCAAGGGGGG
AAGACTGGGGAGGGGGATGGACACATTATCGCTCCAGCACTCTTGTTTCA
GCCTCAACAACAGGAAGAGAGAACCCACAGGCAGTTAGGCCATGTCCATC
AAATGACCCCATATTGTGGAAGAATTGACATTGCACTATGCCCAAGAGAC
TTGGGTGGACATGGTCTTGGGAGTGCTTGAGCCGTCTAATTTCTCAGGGT
CACACTCCTGTAAACAAATGCACTGGCCAGTGCAATCAAATGTGCCATTT
CTAGGACCAAAGTTTGTATATTCCTTTTTTAATATTTTTTTTCACTTGTGT
TGATCATTTGCCTTAAATTAACCTTTCTACTTTGTTTAAACATGGAGAAT
TAGCAAGCTGCCAGGAAGCCAGGCAGGGAAACCAGGATGTTTCCATTTAC
CTTGTGCTCCATATCCTGTCCCTGGAGGTGGAGAGCTTTCAGTTCATAT
GGACCAGACATACCAAGCTTTTTTGTGTGAGTCCCGGAGCGTGCAAGT
CAGTGATCGTACAGGTGCATCGTGCACATAAGCCTCGTTATCCCATGTGT
CGAAGAAGATAGGTTCTGAAATGTGGAGCACATGTTGTTTAGGTATAAAA
TCAGAAGGGCAGGCCTCGTGAGGCAAGGTGGCAAATTTGATTTCTTGGA
GGACACCTGAGCATATACGGTCAAAGTCTGATGACAACACCAGTAGGGAT
GAAGCTGGGAGTGGGGTGGCTAAGAACACTGGACCTGACACTATTAGACA
TGGGTTCCAGCTTCAGGTCTATTACTGCTCACTGTGGCCGAGCAACAGAG
CTACTTAGGTAAAATGGTGATGGTCATAACACTAGCCACAGGGAGGTTA
CGAACCTCTGGTGACAATGTAAGTGAAAGGCCCTGAGAAAGAGTGAGGG
AGTTGCAAATGTCAGTAGCCATCAAGATCTTCTTTAAGAATAGTTTCCAC
TAAAGAGATGATTGCTTTGGTTTCCAGCCTTCTTTGTTTTGTCTCCCCGC
TGGGCCTTCTACCTTTAAAGGGCTTTGGCTCTGGGGGAATTGAGTTGGCT
GGGGCTTGATGACTTCCAAGAGGACACAAGTGGAGATCTACTGCCTGCTC
TTGGCTAACTACCTTCTTCAAAGATGAAGGGAAAGAAGGTGCTCAGGTCA
TTCTCCTGGAAGGTCTGTGGGCAGGGAACCAGCATCTTCTCAGCTTGTC
CATGGCCACAACAACTGACGCGGCCTGCCTGAAGCCCTTGCTGTAGTGGT
GGTCGGAGATTTCGTAGCTGGATGCCGCCATCCAGAGGGCAGAGGTCCAGG
TCCTGGAAGGAGCACTGCGGAGAGAGCGAGGGAGGGAGCCTGGTGAGGTG
GTCCTGCCAGGAACCATGCTTTGACATCAGAGAGTAGAAAGCTCAGAGAG
GAGGAAAGGGCTTGAAAGAATCCCGAGCTTCTAAAGATCATCCCTCTCTG
GGCCAGGCGTGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAAGCCGA
GGTGATGAATCATTTAGGTCAGGACTTCAAACACAGCCTGGCCAACATG
GCGAAACCCCTTCTCTACTAAAAATAAAAAATTAGCTGGGTGTGGTGGG
GTGCACCTGTAATCCTAGCTATTTCAGGAGACTGAGGAAGGAGAATCGCTT
GAACTCAGGAGGTGGAGGATGCAGTAAGCCAAGATTGTACCACTGCACTC
CAGCCTGGGCAACAGAGTGAGACTCTGTCTCATAAAACAAAACAAAACAA
AACAAAACAAAATAAAATAAAATAAAATAAAAGATTATCCCTCTCTGAA
GCTCAAGGAGGTTAAGGGTGTACTCAAGGGCACACAGCAGGTTAGAGGCA

GACTCAAGACTAGAATGTTGGGCTTTCTGACACCTTACAGGCTATTCTTTT
AGAATAAATCCCATTCTACTTTGTTTCATCTTTTTTGTACATGCCCCACC
TACACCATAACATGTATACCTTCTCTATATCTTTTTGTATCCCTAATGCTG
TCACACTATGATTTGCTTTTTTCATGCAGATGACCATAACATTTTCCATT
ACCTATGCTCACTCAGCAAGTATTCAATTTTTCTACACTGTTCTTTTTT
TCCTTTTTTCATAACACTGTCTCATAGGCATTCTGCAAATCCTGTGAGAGT
ACTTTTTGTGAAATGTTACCACTTTCTCTTATTTCAGAGAAGCTCCGTAT
TAAGGCTTCACTGAGGTTGCCTTAAGGCATGATAATGGTTCAAAGGCTTG
AAAGACAGTTAAAGAGACCTGTAAGTGCACAAAAGAAAGTTGAGCAGGAG
AGAATTTCTTGCTGGAGCAGAGCCAAGCTACTGGAAGAGGCAATGGGGG
CAAAGGCCAGGCAGACAAGCCAATGGGCTCCTCCACAGCTGCAGCCAAC
AAGTTATGCCAGTCTTAAACTTCTAAAGAAATATGTTTTTAACAAGATT
GAGGACTGGATTATGAGGCTAGGGGAGGCTATCACAACTGGAATAAAAT
AAAGCCAGAGAAAAGTGGCTGCCTTCCAACCTGCACAACCTGACCTAGCTA
GGCTGATGGCTGGGCCACCTAGGAAGGCTACTGAGCATCATATAAAACAG
AAGGGACAGCAGGAATATAACATGGCTCTTTGTAAGGATGAGTCTGAAAA
ATGACCATTGCTGCCCAAATGCCCTTAGCTACAACCTGAAAATATTTTCAG
AACTGGAGGTTGCAGGATGCTGGAATCTCAGAGATCATCCAGCTCAGCCC
TTTATTTTTTCAGATGAGGTCCAAAGCGGGTAAAATGACTTGTCAAGGTCA
AACAGCAAGTGAATGGTTTTCTTTCAAGTCTCAATTCATCTTTTTTGTTTA
TATCATCTATGTCTTGTTGTTATAAGCTTCACCCAGGTAGCAAAAACT
ATTCTACTCAAAAGGGGTAGACATATGTTAGTTCTCAAGATCATCTCTTG
GTTTCAGAGTTTAACTCAAGTGATTGGCATAGGCTGAATCCATCTCTTAA
AAGGATAATCAAATTTATGTTGAAGACTTGGTTGTCTTCTACTATGAAA
TGGGAAACATTATCACTACTCCTCCCCCTGTCACCACCAAGTGTGGCCACC
ACCACCAACGTTAGTGAGTGACTGTGGTGATATGATGACCAAGTGGCCAG
GTCAGCAAGTGGTGCAGCCTGTGTCTCACTGGAAGAGGTTAAAGTCTTTC
TAAAACAAAATACCATGGCATCAAAGTGGCCAGAACTCCCTTCTTTGAG
CTTTCCCTGTGTTAGAGCCCTTCTTGGGTTGGGAGTTAAACCCATAGTC
TTACCTTCATCTGTTTAGGGCCATCAGCTTCAAAGAACAAGTCATCCTCA
TTGCCACTGTAATAAAAACAGGGACATGTCTCAATTATGTCTTCTAAACA
GGTTTATTTTTCTTCCCTGTGTACAAGACTTGACTGTTTCATAAGAACT
GCAAACAGCCTGCCTCTCAAAGCTGCCTGAAACACCTGGCAAGTTTCACA
GTGATATGCGCAGAACAGTCCAGAAGGCAGATTCTAGGCCTGGCAGGTGG
GCACCTTGGGTGCTCCCTGTTGGATCTTGAGGCCTAACCTCTAGCCCAGC
AGAGTCAGCTAAAATCTGAGCTCTCCCTCTCCCTCCAAGCCACACTTTGC
AAAGGGATTCTTGTATTGTGGGCTTGGAACTCTTTCTCCCCATTTGCCT
CTGCAGGAAGCCCTTGCAACAACACATCTGGATAGCCTCCAGGTCCCAAG
GCTGGAGGGACTTGTAATGGGAAAGTAGTCTTTAAATCAGATTTACTTGG
CACCTGTTTGGCACTGAAAGAGGCAATTTAGGGGAAAAATCTGGTCTCC
AAGCACAGATAACACTCTACTCTTGAAAGAGGAGACCTGCTCATGTTACT
GGTCTCAGCGTCTCCACTGACCTGTAATAAGCCATCATTTCACTGGCGAG
CTCAGGTACTTCTGCCATGGCTGCTTCAGACACCTGTGTAAAAGGAGAA
AATGAGTGACTTCCCCATGACGGCTACGTTTCATGTGTGATTTCTCTCAGC
ATCCAGTGATGGCAGTCATGCAAGAAATGATCTCTGAGTAAATGAATG
AATGTGTGAAAGAGAAGTCTTTGGGTCTAGAGAAAAGCATTGTGCTAAC
CAAACCCCAACTAGCAATGTATTGGCTAGGAGAGCTGGAGCAGAGGCTTT
GACACTAACCTTTAGGGTGTGAGCTGTTAGATAAGCAGTATCCATTCCCA
GAATATTTCCCGAGTCATAAGCATTATATTACACCTGGCATTTTTTGCAA
AAGCTGAGAGAGGGAGGCAGAGAGGGAAGGAGAGGGAGAGACAGAGAAAG
AAAGAGAGAGAGAGAGAGAAATATGCATACACACAAAGAGGCAGAGAGACA
GAGAGACTCCCTTAGCACCTAGTTGTAAGGAAGATTAAAGTCATACTTGA
GCAATGAAGATTGGCTGAAGAGAATCCCAGAGCAGCCTGTTGTGCCTTGT
GCCTCGAAGAGGTTTGGTATCTGCCAGTTTCTCCCTCGCTGTTTTTATAG
CTTTCAAAGCAGAAAGTAGGAGGCTGAGAAATTTCTCTGTTGAATACCTG
ATTTCACAATCAAGTTAAAGGAAAGGGGAAAGAGTATTGGTGGAAGCTT
CTTAGGGGAGGGGACTAATAAACTGAGATAATTCTCTGGTTTCATGGAAGG
GCAAGGAGTAGCAAACCTATGACACATTTTGCAAATGTATCACCATGCAA
TATGCATTGTTTTCTGACAATCGTTGTGCAGTTGATGTCCACATTAAAA
TACTGGATTTTCCACGTTAGAAGAATGTTTAAATTTAGTATATGTGGGA

FIG. 4 (49 of 61)

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CAAAGTGGAAGACACACAGATTTATACA. GCACATACTTTTCTTCATTCA
CTTCTTTGTACTTAAGTTT TAGGAATCTTCCCCTTACAGATGGATAAATG
GGTACAATGAAGGGCCAATAGCCCTCCCTGTCTGTATTGAGGGTGTGGGT
CTCTACCTTGGGTGCTGTTCTCTGCCTCGGGAGCTCTCTGTCAATTGCAG
GAGCCTCTGAGGAGAAAATTGACCTTTCTTGGCTGGGGCAGAGAACATAC
GGTATGCAGGGTTCAGGCTCCTGACGGAGTTGGGGCAACCCTGGAGATAA
GCTCACACAACCCTGCAAGACCAGGTGCTGTTACCCTAGCCAATCTCATG
GATGAACCAGATCAATGCCAGATGAGCTCTGCCTAAAATGATTTTTTGGT
GAACTCTGAAAAGTGAATATTGTTTCTGTAAAGAAATATCCATCTGAGACT
CTATCTCTTGGTAATACCAAGAGTTATCAGTTTCTCTTTAACCGAGACAC
CAGCAAAGTGCCTGCTCCAGGGTACTGCCCAGGGGAGCCCTCCATTTGTA
GAATGAATGAGAGTCCAGGTTATGAACAGTGCCTGGAGTGTAGGAACACC
CTCCTTTGCCTCTTTGACAGGTCTGCATCATAACACTTTTTTTTTTTTTT
TGAGACAGAGTCTCACTCTGTCTGCCCAGGCTGGAGTGCAGTGGCACGATC
TCGGCCCCCTGCAAGTTCCGCCTCCCGGGTTCACACCATTCTCCTGCCTC
AGCCTCCCCAGCAGCTGGGACTACAGGCACCTGCCGCCACGGCCGGCTAA
TTTTTTGTATTTTTAGTAGAGACAGGGTTTCACCATGTTAGCCAGGATGG
TCTCGATCTCCTGACCTTGTGATCTGCCCCGCTCGGCCTCCCAAAGTGTT
GGGATTACAGGCGTGAGCCACCGTGTCCAGCCTGTAACACTTCTTATAGC
ACTGAGTTGAAACCTTGCTCCTCCTGGTTCCTCCAGGAACTGAAATCTT
TTTGAGCCAAGTCTAGCACAGTGCCTGGCATGTACATTCAGGTGGTAGAG
TTTGCTGCTTGAATGGGTGAATGGGAATTTGACAGCATTTTTATTCAAAT
TAGTATGTGCCAGGTATCGTGCTCGCTCTGCATTATCCAAGGGAGTGAGC
CTCTGTGCAAGTATTTGAGACACGAGGGAAATAGGTCTACTGTGGGAAA
AAGAGCATTTTCATGGAATTGCTCTCCAAGCAGCCTTCTGATTTTTAATTT
GGCTCCCAGTATCTTGATATCAGGAGTCAGTCACAAGAACTCCATCTTTA
GTAAGTTATATTTTCCACAGGAAATCTAAAAGCTGTTCAACATGTTAGTT
TCCTGTGAATTTGATAAGCCATAATCCATTCTTAACACTGAGCCCTCCTG
AAATTTGGTGTCTGGTCCTGCAGATAGCTAAAAGCCCTGTCTGGGTGGCC
TAGGGGACTCCTCTGTTTTGCCTCCACAGGATCCACTTTGCAAATTAACC
ACTGGTTCTCCCGTTGTAGGAACTGCCACCTTCCTCAGAGCCTGTCTTTC
TTCCTTCCTTCCTTCCTTCCTCTTTCTTTCTTTCTTTCTTTCTTTCTT
TCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTT
TCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTT
TTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTT
TTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTT
TTTGTCTCTCCCTCCCTTCTCTCTCTCTTTCTTTCTTTCTTTCTTTCTT
CCTAGACAGGATCTACCTTTATCCCCAGGCTGGAGTGCAGTGGTACAAT
CATGCATTCAATTGCATGATCACAGCAGCCTCAAACCCTTCCTCAGAGTCT
TTATGCGGCAACCAGCAGGGTCTGGAGGGTTGGTGGCTCTGTGAACTCTC
CTGACAGAACACAGAGATGTCTTTGGTCTGTTGATGTGATTACAAGCTGA
ACGAAGGAGGATCAAAGCCAGTGACAGGAAGGGAGATATGCAAGGGACCC
GAGCATCAGCTCTGAGTTAGTCCATTCTGCTTCTGGGACTTGGGATACAG
GTCAGAAACCTTGAGCTTCTACTTCTCCATCTTCCAATTGTAGCATCCAG
GACCTCAGAATCTGCCAGCTAAGAGGAGCCGTAATGATTGTCTGGTGGGA
TATGGTGGGACCACAGAGATGAAGACATGAATAGCTATTTGAATGTGAAC
AGCAGACGAAGAAATCAAGGCTAGGAGGGTGGAAAGTGAATCATCCAATAG
CACAGTGTGGTTGAAGCAGCACTAGTATCCAGGTTGCATGAGCCCCCTGAT
GCTTTTCGCTCGAGGGAAATTTTGGAGCCATGGGGCAATGCCCCCTGACGT
AACAGTCTCCACAGTTCTGCCATGTCTCATCCTGGCCCTGTAACCTGGAC
CCAAATCTGCTACCATCCCATCCATCTCAGGAAGTGAAACCTCTTATGTC
AAATAGGTTGTGCAACGTATGTATCAGATCCTGTCTTCCCAAGGAGACCG
CTCAGGCCACAGCACTTCCTTCCGATCCCCAATGAGCAGAAAATATCTCG
CTATAAACATAGTTGGCACTAAGGGAGGGAGTGGAAGAGTGATGATGATG
TAGATGGTGTAGTGTAGCCCCAAGGAAGTGGAACAAGCAGAGATGGGGAGCT
GGAAATGCCAGGATGCTCCAGCTTTTGGGGAATTATTAGCTCTTGAGTC
ACTAAAGCCTTTCTCAGCTGCAAGTTCTTCTTTACCCTGTCAGGTCATTC
TTCCAAGACAGGAGACTGACATTTATTCAAAGCAGCAAGTGCCCTGATAC
CATCTTGTGTCTAATCATGGGCTTCGCAGCCAGTTATCAAGGTTGATCTC
ATCTCATTTGGTCTTCAATCATTTTGAACAAGAAGACAAGCAAAATAATCA

FIG. 4 (50 of 61)

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TGGGTTAGTTCTTATATTATTGTGTGTACATGCAGTGATGTCTGTTCTTT
GTAGTGAGCTGTTCTTCTTGTTCACCTCTTGCTTAGAACAGAACTAA
GCAATCTGCCCCAACATTTTCCCCAATTTCCCATCTCATTCTTGGCACT
GGCTTCCTAATATTTGTTCTTATGAGTCATTTTCTTGTATCATTTCATG
AGTCCCTCTGGGATCTTAAAGTATGAAAAATGTTGTGTGTACCCACACCT
GTCTTTGTGGATATTTCTCTCCTTTCCCTTCTGCTTCTGGGATTATTTGG
GAATGGGCACTATGATTTTTATCATATCGCTTCCACTTCCTTTATGGCAT
CATCTCCAATGGGCTTCTTCTCCCTCTTGATCCAGGTTCTCAGATTGGG
GACATGCAGAGTCCAAGGAACATTCCATTCTCCTCCCTGGTCTAGAACAA
GGAGGGCTTAGATATATGAGCAGGTGGCTGGGGCTGGCGAGCTATGTAGT
CTCCAATGGCTTTTCCCTGATGTCGGAGTTGTTATGTCAGTTCTGGGAGA
CCAATAAGACCTTGTCTTCTTGGATCCATCAGAAAAAGCCCCCTGGGT
GGGTAAGATGGATGGCAGGGCTCTCCTACTCTATGTCTTTTCTCACACCT
AGTGGGTATAAGAGAGGGGACCACAAACAGAGGGGGCTCTGGTACCACTT
ATCCAGGGTCTGGAAACATTTTCTGTAAAGGGCCAGATAATAAATGTTTC
AGGTACAACACTCAACCTTGCATCATTTCAGAAAAGCAGTCAGATAATA
CATAAATGAATGGGTGTGGCTGGACTTGTCTGCGGTCCCCTGTCTTATA
TCATTGTATTATATCATTTTTTTCTTACATACAAATTTAGAAGCAATACTT
AAAAAAAAAAAGCCGTCCTTTATTGAGCACCTACTAAGTGCCAGGTACCT
TTTTTCCCTCATTATCTTATTAACCTTTCATAATAACCTTTAAAGTAGA
TAATATTGAACCATTTGACCTATGCAGAACTGAGGTTGAGACAATAAAT
TATTTAAGACCGCACAAACAGTAAATGCTGGAACACTACGACTCAAATATGG
GTTAACTGAACCAAACAGATCTTTATTTCTCACTTTTAATTGTTACAT
ATGTTTATTGCCTCATCTCCTGTCCACATGGTGCCCATCGGCAGACTCCT
TTCTCATTCTCAGTGATTGAGTGACATTCTAACTACATTGGCCTGGCAG
ATTCACCTCTGTCCCCTAAATGTTTCCACATTGTCTTTTAGGATTGAGA
TCCTCTCTGTTCCCTTGTCTTCCCTCCTTTCTTCTTCTGGCGGTGACGTG
CTGTGTGAATTTGTTTCTTCTCCTCTCAGGGTAGTACTGGGACTTTCCA
AATCAGGGTTTTTAATGATCTCTCTTCTTCTTCTGAATTTCTTCTTAT
TCCCATTCACCTTCTCATCTATAAGTGGCANCTTTGTTGCTGGAAGATAT
CCCTTGTGCAGGGATTNCTCTTTAANAATTTGTCNNNACC

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GTGATCGTCAACCTCCCACCCTGTAGGGCCTCAAGCATTGAGGACAATCA
CTGGCTGCCCATTAACCCAGAAATGTTGCCGAGACAGGAGGCCGTGGCCC
AAGTTCCTGGAATGGGGTATTATTATGTCAGCACAAAGGCCCTTGCACAA
ATGAAGGCTTTAAAAATGCAGTCCTAGTCAGGTGGAGGAGGGCTTATAGG
ATTCCCAGGAATCTGGATCATTCTCTTGAGAGCTTTCCCTTGTCTCTGTT
AAAACCTCACATCGTACGGCCCAAATAACAACAAAAAATGGATGTAAATTC
TTGAAATAACTTGTGGATGGGGGAACAAGGCCCAACCCCCAGATCTGCCA
GAAGCTTCAGGTGAGGGTCCCAAATGCCAAAAAGTCTGGTATCAGAGAGG
ATGGCCAGTGACNTGGGGACACATGCCCTTTGCTGTGTCACTCAAGGAGC
AGCAGCTTCGGCCCCGCACAGTGACCAGGACCCTGGCTTCCCACGCTGGG
CAGGAGCTGGTGTCTGATGAAGGGAATGCCTGGCAGCACGTGCTGTCTGT
CTCCTCGTGTCACTTACCTGGCTTTGCTGCGAAGAGGCCACTTGCAATTT
CTTTATTTTTTATATTTTTTTAATTTTTTAAATTTTTTATTTTATTTTA
TTTTTATTTATTTATTTATTTTTTAATTTTTTTTAAATTTTTTAAATTATG
CTTTAAGTTTTAGGGTACATGTGCACATTGTGCAGGTTAGTTACATACGC
ATACATGCGCCATGCTGGTGCGCTGCACCCACTAATCGTCATCTAGCAT
TAGGTATATCTCCCAGGTTAATCCCTCCCCCTCCCCCACCACCAAC
AGTCCCCAGAATGTGATGTTCCCTTCCCTGTGTCCATGTGATCTCATTGA
ATTTCTTTAAAGGTGGAATCTCTCAGTGGGGTCTAATCTGTTTCAAGAAAT
TCAAAAGAGTATCCTTGGGAATGACTGGAATTCCAGAGTCATCTGGTAAT
CCTCATAAAACAACCTCTGGATGTCTCTCAGCACATCTCCCACCTTGAAC
GCAGGAGGCTGGTTCAAATGGAGGAGCATCGCTCTACTGCACTTTTTTTT
TTTTTTGGCCTAAAGTGCAAAAGGGGATACGTTTCATGTAAATAAATCAA
CTGCAAATCGCTAGTTATGCTGAGCCCTGTCCCGTGCTGTGGACACAAAG
GAACCAAAGGCTTTTCTCCCCGCCCAACACACACATAACACACACACAAA
ATCATAAAACATACATACCCCCAACACATAACAACACACACACACACA
CAAAATATATACACACACACACACCAACATGCCACAAACCTGTGTCC
AAAAATAAATCCTACTGGTGGGTTTGTGGTCTCCCTAACTTCAAAATGA

AGCCGTGGACCTTCGCACTGAGTGTTACAGCTCTTAAAGATGGCATGGAT
CCAAAGAGTGAGCAGTAGCAACGTTTACTGTGAAGAGCAAAAGGACAAAG
CTTCCACAACCCAGAAGGGGACCCACAGGGTTGCTGGTTGGGGTGGCC
AGCTTTTACTTCCTTTTGGCCCCCTCCCATGTTCTGTTTCCATCCTATCAG
AGTGCCCTTTTTTCAATCCTCCCTGTGATTGGCTACTTTTAGAATCCTGC
TGATTGGTGCAATTTTACAGAGTGCTGATTGGTGCGTTTTACAATCCCCTT
GTAAGACAGAAAAGTTCCTGATTGGTGTGTTTTACAATCCTCTTGTAAGA
CAGAAAAGTTCCCCAAGTCCCCACTGGACCCAGGAAGTCCACCTGGCCTC
ACCTTTCAACTCCATAATGGCATGAAAATACATATGTTGTACAAAACATA
CATACACAAAGTATACATGCATCTCCCCAAATATACACATACCACAGAAA
CATACACACAGGAACCTCAGCTACCTGTCAAAAGTCTGCATGGTGATTGCC
TCTGCAGTGAGTAGTTAGAAAAGTGAATTTGTTTTTCAATAAATTGGAGT
CCTTAAAAATCGTTGTAAGATAGAAAATTTTTTAAAGTATATAAAATAAA
ATATGTATGTCCTTTGGTCTAGCATTTACACATGTAGGAATTTATCCTAG
TGGAGTAATCAATGATATATGCAAAGATTTGGACAAGCATATTAAGCACA
GAATTATGTATGCATATGTGTGTGTATATATATATATATCTEATACATAT
AATAATGTAAAAGTGAAAATAACTCAGATGTTCAAAATTGAGGATTAGTT
AGACTATGATCTGTCCATATGTGACATACAAGTTAGCTGCCCCCTTATTCT
CTCGAGCTTCAACCTCCTATAAACAGTGTCCCTTGTATATCAGTATTGGT
ACAGATAATCGAACTTATTGAGGTTTTACATGGGGCAATAAAGGCAAGAG
TTTATGAATACTCCATACTACACTAGGTAGCACCCCCTATTAAAGACAAA
CTCTTCTCTCTCATTTCCTTCCCTTCCGGAACCACTTGGTTGAATCTCT
ACAAGTCTCTATTGCAACTGCCTCAACATGGCACCCCTCCCTGCATCTCCA
TCTTCCCTGTCTGAGAGCAATGGCCTGCTGCCCCCACACTCACATCCTC
ATTCATTCCAGAAGTGAGCACACAGAAAGTGCCTACAGTTACCCCAACCA
CCTTCTTAGAAGATAAGTTAGTGTGTTTGTGTTTACTTTTTTAAATTTTTAC
TTCCTCTTTTCTTCCACAATCTCATCCCATCCCAAGAGGTTTATCAAGAA
GTTCTCTAAAGATATGTGTCTCCTTATGGAATTTAACAGAAATCAGGGAT
TTGTATTCTAGCCATCAAGGGAATAACATTTTTCCAGGTCTTTAGACAAA
TAATGGAATACCTTGCAGTAATTAGATACACTATTGTAGAAAAGTATTGA
TGAAATGGAACGATGTTTGAGATATCATATTGAGTAGAAAAGGCAAGATA
CATTAGTAGGAAATGTATCTTACAAAATAATTTGTCAGACACACTCCTA
TATTTGTATGTTATATAAATGCGTATGTGAAGAAAGGCTAGAGGATGAGA
CCACAGTCTTCGGTGAAGTTTAAGAGATGAGGCTGCAGCATGCTCAGAAA
GGCCTGGGTTATAGTTCTTCCAGTAATTAAGGATGTGATCTTGGGTAAAT
TGTCCATCCTCTCTAAACTGCACCACCTTTTGTCTGTAAAACAGGAAGGA
TGGTATTTACCCCCAGGGTCATCAAAGGATTTGGTTGGAGAAAAATAAAT
AAATGGGCTGAGCCCAGACCTGGCACAGTGAGAGCACAGTGGTTGACTAT
TGTGCTGGCCTGTTGTTCTGTGTTATTGACATGCTGCTGGTGGTGGTCC
AGAAGCTATTACCTTAATTGGTTATGTGGATTTCCCCTCATACTGAGCAG
CTGTGTGTGGTGTGTAACATAGCCATACACAGTAACTGACAAGGGCA
AATGTGATGGAAAAATGCAAGGAAGTGCAGATAAATAGCTAATGGGCTGT
AGAAGGAAGCTAGTCCTTGGAGGGCTTGATCAAGGAAGGTCCTTTTGCAT
GTCACCTTTGAAGAAGAGGGGACATAGAAGAGGTATAGTGCATCCCGGAG
TGTACCTGGAAGGGAACATGAAAAGAGGACATTTTTCTCTGGGACATGGG
GACTCCACTTGCATGAACTCTGGAATTGGGGCAAAGAACCATCATGAGAA
CAAGGGCTTCCTTGAACCTCCAGGCTCATTGGCTGATCTAAACCCTGTG
TCCCCTCTTTCCTTCACTCTCCTCTGTTTTCTATACCTGTATTATTGGAC
TGGACTGGAAGCCACCTGATCTATACAAGTACCTTGAAATGTGTTGAAT
AGGTGTGGCACAGTCCTTAGCAGAGTGGCACTACCCCCACAGGAATTTGT
TTATACCTTTGGCATGGAAAATAGCAGGAAATGAGTGATCACTGATAACT
GAGGATGCTATTTATTATTGGCCAAAGGAATACTTGTGTTGTATTGTCAT
AACCCTCACAACTGTTGATTACAAATGAGTACCAGACCTAGCTCCTTC
AAGTAAAGGATCCTGAGAACTGAAGGCAAACAGAGCTCCAGGAGTCCAAG
ACAGAGCCACAGACCAGAGGATCCCTGGCCCAGGTAGGTGGTCCTCCTG
CACTGGCTTTCAAGGCCAACAGGATGGATGGGGAAGTAGAGTAGCATCTG
GCCATCTAGACCCTTGCTTTTTATCCCCACTGGAAGCACATCTGAATTC
TAAATATGATCTCTGAGACCTGCCCAGAACACCTTGCTCTCAGCCCCAGT
AGCAGCCTGCTCTCTCCCAGGAGGGCTTCCACTAACAGTAGGGCATTGC
TGGAGGGGCCAGGCAGACACTAGCTTAGGAAATCCACCAACCCTGGAAATG

CTAGTCCCTTCTCTGAAGGCTCAGAAGACTGACTTTAGAGTCTAGAAAAT
ATTGGTCCCTTGGGAACAGATTTTGTAGTGCAAAGAGATGGACTTCAGATGG
CCAGATGCACTGCTTCTTTAGGGAATTCTGTGAAAGCTCCCTGCATTTAT
CTTAATACAGGCAGCAGATTTTCATGAGTACCCCCGAGGGATGGCCCCAGG
TCCTCCAGCCTGTGAGCATCCTTCTGTCTTCAGCAGCACCACAGTATCT
TTATATGTCTTTGGATACCTACGTTTCTGCCAGACATCTCTTGCTCTGAT
GTCTCTGGCTGCCAAATTCTCTGTCAAGCGCCTCCAATTTTTTGTGTCTT
TGATTTACCCCAACATGACAAAGGCAGTTGTGCTTCATGTATTCAGGGAT
ACTGCCAAACCACAAACAGGTTAAATCAAATAGCAGATATCCCTGTTCC
TAAAGACCCATCAGCTCTACCCACCTGCTCCTGCTCACCGTCTTATTGT
TGAGTCCCTGAAGCCCTTCCTTGTCAATTTTTTATTTTTTGCATGAACAATTT
AGTTCCCTTTGTCTCACTCCTAAACCTTTCTCAAAGGATTGGATTTGTAC
ACAAACTGCCTATCTCTGCAATCTTAGAAGTGATATGATTCTGAACAAAT
CACTTAACCTTTTGATTTTTTATTGGTAAGATGGGAATACCAATTTTTTGCT
CCACTTCTGTCTATGTTGGCCTGGGCTGATGTTGAAAGCTCTCGGTCAA
CTGAGATAGGGTGTGCAGAAATTTATATATATAAATATATCTCTCCAACC
CCTCCCAATGAAGCAAGTCACGTGAGTCAATCCTACCCTAAGATATTAGG
GATTGAGCCTCCTGGGACATTTGGTGGCTTAGGTTTTTCATGAAAAGAGGT
TGCAGAGCAACTGCTTTTTTGTAGGCAAAGATTAGGCTACTGCAGAGACT
CAGCAAACCTTCTATAGAAGGTGTCAGATGGTAAGTATTTTAGGCTTTGCT
TGCCAGATGATCTCTCAACTAGTTAACCATGCTATTGTAGCCTCGAAGCA
GCCAGAGACAATATGTAAACAAGAGCATGGCTGTGTTTCAATAAACTTT
ATTTAAAAAACAGTCAGGGACCGGATTTGGCCAAAGGCCATAGTGTGCC
AGCCCCAAGACTAGAGCAATGCACTTTTAACTTTTTTATTTTATTTTGT
AAAATGCCAAGATCCACAAAATGCTATTGCACCCCGTGTGTAGCACTG
TGACTCAAGGTTTGGGAAATTCTGCTTTGAAGGCGTGATAGACAGGAGAG
CATGGTCTGGCCCCCTTGGTGCCTTTCTGGTTGCAGCGAGCATTTCAAAC
ACAGAGCAAGGCCAGTGGTCTGTTGAGCACTAGAGACATGCAGCAAGGTG
TCCTGGGGTGAGAAGATGCCATAACTGGTCCCCCTTCTATCTCCTTAGGT
CTTGGACTTCATTCCATTTTCTGTTGAGTAATAAACTCAACGTTGAAAAT
GTCCTTTGTGGGGGAGAACTCAGGAGTGAAAATGGGCTCTGAGGACTGGG
AAAAAGATGAACCCAGTGCTGCTTAGAAGGTAAGGTTCTTGTAGAAATC
TACCTCAGGGCCAAAGTGTAATTCCTAGAGCAGAACTTTGCTAGGTGCTG
TGCACAGACCCAGTTGTTTCTGCTGACTTGACAGTAAGTGAGCTTTCA
AATTTCCCTGGACAAATAACTAGACAAGAGAAATCTGGAAGAGAAAAGG
AAGCTTTGCTTCAGTGTCCAGGCACATCAGGTAGTAGATAAAAGGATCGT
CCTCACCTACAGATTTGGGGCTTTAGCATCCTGTTTGCCAACTGGATGGT
TGCATATGCTTCAAAATGCACCTCTTCCCTCCCAACATTCCCAAGTGGAA
GAGAAGCCTCCGATGAGAAGGAACCTCTAAGGCTGGGCTGAACAAATGA
CCCAGGCACAGGGCATCTGAGTATTCATGAGGAACACATTTGGGTGTTG
CCCATGGGGGACAATAGGAGGAGGCTTTTGACCCAAATGATTGTCTACTG
AGGTGTGACGGGAGAGGCCTGTGACATGCCAGAGGCCAAACCCGTGATCC
AGTTCATCTCTATTCTATGTTTCTGAAGAGGGAAGCTATGATTTAATGTC
ATTACTATCATGCTGCTCTAGTATTTCTCAGCACATACACAGAAGAGGGA
ATTAAATGGTCCTTGATACCCCTAAATCCTTGGAAAATCCGAATTGCATA
TGCTAACCTCACTGCGTCTGACTGCAGACCCGGCTGTAAGCCCCCTGGAA
CCAGGCCCAAGCCTCCCCGCCATGAATTTTGTTCACACAAGTAAGGCCTC
GGGGTGAGGTGATGGGGGTGGCTGAGGTGCGAGGGTGGGGATGGGGGATG
GAGCCATTGGGTCTCTTACAGGGTGAGAGAATTGTAGAATGGGGACACC
TAAGGGTGCTGGATGGGGCTGAAGTCTTTCTTTGTGGAAGCAAATCCCA
TTAGGAGATAACTCTGGGAAAGATGAGCCCGGGGAGGGGCAGGTGATGCT
CACCTGCTAAGAGGCAAAGGGCAAGGAAGAGTTTGTGCCTGGGAACCTTC
CAGGTGCCTCTTCTGACCATAGCCAAGAGACTGGAGACACAGACCTCCTC
CCAGCACTGAGGACAAACAGCCATGGGGCCAGTGGGGGTGCAGGGACACC
CACACCACTAAGGGCTCAGGGCGGGCGCCTTCAGAGCCTGAACCTTCCTCT
CATGCTGCCATTTGAACACCACAACACCTAATAGGAACTGTTAACATT
GCCACTGTTCAAGGTGTGGAACCGAGACAGACAGTGGAGATTCCCTGCCC
TAGGTGACACAGGTAATAAGTGACAGATGTGGAAATTTAAAGGTACTATA
ACGTCTCTCTGCTGACTCAGGCTTAAGGCTCCCATCACCTCCTCTCTC
AGGACAGAGTCAGGAGGCCTCAGCCTGAGCCCCAGCTCTAGTGCAGGTTC

FIG. 4 (53 of 61)

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ATGTGGGAATACTGAGCCTCACTAGTACAAATGGCAGAGAGGACCAAATGG
GACCAGGTGTGTAAGGGTGCCTGGCACAGTTGGGGGAGGCTGCTGTCGCT
TCTCCACCGCTGCTGCTGCAGTTACCTTTGATGTTTTAGTTTTGTTGTAG
TTACACCATTTGCTGGCTTTGGATCTGCACTGTGTCCACTCCAGGTGGAAC
CACGCACACAAGCCTCTCTGTCGGGCCTGTCCTGACTTCTCCTTGTTCAGG
GCTGGGATCTCCTTCAAATCTGGCGGAAGTGGTTCTCCAAGTCTGGTCCT
CAAACGTCAGCAGCATCAGCGCCTAGAAGTGTTAGGAATACACATTCCCA
GGCCCCACCACAGACCTCCTGCCTCAGAACTCAGGGCGCTGAGGCTCTA
GGGGCTGCTTTAACAAGCCTTCCAGGTTATCGTGACGCACCTTGAAAGTC
TGAGAGCTACTGCCCTACAGAAAGTTACTAGTGCCCTAAAGCTGGCGCTG
GCACTGATGTTACTGCTGCTGTTGGAGTACAACCTTCCCTATAGAAAACAA
CTGCCAGCACCTTAAGACCACTCACACCTTCAGAGTGGCCTTGAGAAAGA
TTTGGGGTCAAGGATCATGAGCGAGAACACCACTTAAGAGGATAGTGAAC
TAGTCTGCATGTGAGACGCTGAGATCCTATGTCAGGCTGTGATAGGAGGG
AAACAGAAACCAAAGGAAAGAACAGCTTTAAGAAGCGCTTAAGAGGTACA
AAGTAAAATGATGGTGCTAGAAAAGTAGCTTCTTAAAAAGAGCATTTC
AGTCTCACCTGGACTAACTGAATGAGAATCTCAGGAGTGTGAGGCCAG
GTATCCATGGTCTTAAATGCCACCCACCAGGTGATTCCAGTGTGCACC
AGGGGTGAGAGTCACAGCCTTAGGCCATGCCACTCAAAGGGTGTCTTCAG
ACCAGCAGCACCCACAGCTCTGGGAGTGCATCAGAAAGACAGAGGCTTGG
CACCACCCACACCTACTGAACCATAGTTTGCAGGTGATTTCTTGACATT
AAAGTGTGGGAAATGGAAAAGCTTAGAGTTCAGCTAGCTCGGTGACTCTC
AGTCAACCTGCACCTGCTCCATGAACCTCAGACTGCCTGGGATGGGCCCAG
AAAAGCTCCTGAGGAGATTCTGATGTAAGGCAGGGCTGATAACCATGGAT
CTCATCTGACCCCATATCACTGGGGAGTTACTTAGGATCTTGCTGGGGC
CAGTCATCTCTTCCATAGACACTGAGAGTGTCCACGATGCTTGGGGCACT
ACAGGGTGGGAGGTGGAGGATCACGGGTGAGTCAGATAGGAAGCCTGCTC
CTGGGGAGCTTACAGTGCTATAGGGCAGCAAGCCAAGGATGCCAATACCT
GTGTGCAGGTACCACTGACGAGTGCAGAGCGCTGCAGCACCAGAGAGGAA
GCTACCCTGTGTCAGAGGGGGCTGAGGAGGGCTGCAGGGAGATGACAGGAA
AGCCGGTGTACAGGAGGAGTCTCCCCACTCTTTGGGCATGAGGAGACC
AGGAGGACATTCTACAGTGAGAAACCCAGGCAGAGGCCATGTGCTTATGG
CATGGGAAAAGAATGACACCTTAGACTTATTCTCTACATTAGAATTGCCT
ACCACAGATACCCATATTATAGCTTCACATAGTGTGGTGGTACTGTGTT
TTCATATTGTCACATTTGCCATTTTCCAGCCACCCACCCATTCTTGACAG
TCACTGGCCCAGCCTGGGGGGCCCTGTTCTTTATCAAACAAGTGCCTGAG
CTCTTTGCAGAGGTGAGGGTCACCTGTCCAATCAGAGGCCAGGAGGGAAC
GTTCCCTTTTAAGACCCTACTCTAGGCAGGCCTGGCCCAAATGAGTTGCT
AGGAGCCCACGCCCTAAGAACCCTCTGAGCACTGTTGTGGCTGGTCCTGC
TGCTAGAAGTTGTTCTCCAGGGCCAGGTGCAAGATTTGTGGCTTTTCAA
AGGAGCCACTAAAGCTCCAGCTCAGCCTTGCACGGTGCTGGGCTCCTGGG
GGCTTCCTGCCTCCAACCCTCCCAACTCTTCCATCACCGCTCCCTTAGCC
TGGCCAGTGCAGGGATCTGTTCCACTCTAGGCAGTCTGAGGGAATGATG
CCTCCAGTCAGAGGGTGCAAAAAGAGAGTTAAGAAAACAATGATTATA
AAAAGTCCTTTTTTATACGCCAGACATTTTCTTTGCTCAGGCTAAGTGCTA
CTTATTTGAGTAAGCATTTTAGTTCTCATAACTCCTCTCTCAAGTAGGTG
CTGCTATTACTTTTCAATTCACAGATGAGGACATTGAGGTTTGGAGAGACT
TAGTAACTTGTCTCTGTCTACAGCAGAGCTGGGATTTGAATCTATCTG
TCCAAATCTGGAACCCATTTGCTTGACAGAAAGCTTAATTGCTTGTCCC
AGCAAGATAGAAAGCCTGGGAGTGGAAGAAATATTCAGTGGCTGTGATGT
CTGAGCCACAGGCAGGGTGGAGAGCTAGGGCTGGGGCCCTTGGACGTGG
GGAAGAAAGGGCTGAGTCTTCCATTTTCAATGTGAAGTGTGATATCTGG
TGATATTGATCTAGGTCAAAGGTGAAGAACTTAACCCGAAGAAATTCA
GCATTCATGACCAGGATCACAAAGTACTGGTCCTGGACTCTGGGAATCTC
ATAGCAGTTCCAGATAAAAACCTACATACGCCAGGTGACTCTCAGTTTTG
GCTGTGTTTTCTGCCTCCACCTAGCAGGGGTAAAGGCCTCCTGCTAGGTGG
GCTCAACTCCATGCTATACCATGCCCCATCTCCAGCAGGTGGTGAAGCG
AGGAGGAGAGGCCCCAGGGACTAGGGCATCAGATGAAGGGTCTCTAGCAA
TGACCAGATCTGAAAGTAGTCTTTCTGGAAGGGCTGGAGAAAAGAAGGA
GGCAGACACTTAGACTGGAAGAAGAGGAGGCTTAACCGGTGTGATGGAG

FIG. 4 (54 f 61)

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GGAGAAGTGGACCACAGAGTCAAGGGAGAGGGACTGTGCATCAGGCCTGA
AACCCCAGCAGACAGGAGAGACCTTTCCCTGCTCTCAGAACCCACACATG
TTCTGACTGTCTTTTTCCAGAGATCTTCTTTGCATTAGCCTCATCCTTGA
GCTCAGCCTCTGCGGAGAAAGGAAGTCCGATTCTCCTGGGGGTCTCTAAA
GGGGAGTTTTGTCTCTACTGTGACAAGGATAAAGGACAAAGTCATCCATC
CCTTCAGCTGAAGGTGAGAGTTCTAGCTCAGTTTCCTGGGCCTTTGGCTA
CCCCAAAGTAAAAGGCCAAGATCCTCAATGCCTCTCGCTTTCCTGCAAAT
TCTTATCTTGGCCAATATAACAGGGACATCCACCTTTCTGGAAGCACCAG
GCAGAAGAGCCCCATAACTTCTTCTCTGGTTCTTGGCCCTTCTAGGGAA
GGAGGAGAGACTCCTCACAGCGGGGAGACAGCAAGGAGCTGAGCACCTGT
TCTCCTCTCCTGGGCTCACTGGTCTTGGCCCTGGGCGGGTGGCGGTCCCC
TCCTGCTGTGGCCCTCCATGTGGCAAGCAACACAATTGGGCCAGGACCCT
GGCGTGCTGCTGTAGGGTAGGAGGGTGTGAGGGAGCACTCGGAGGGCAGT
GTGTCTGCCCTGCAAATTTAGTCTGGATGGAGCATCCTTTCACTTGAGG
GGAGAAATCTTAGGAAGCTGAATTAGATACAGATCTAAGCCATATTCTCT
AATTTTAAAACTATAGAGCTGAGATTTTGGTATCCATCTGACTCTTACG
TCTCTCTCTCTCTCTCTCTCTCTCAGTTTATTTTAAATCTGGGGGACA
AGAAGGCCTGGAAAAGAGGGCATGATTGCTTATCATCCCTTAAATACCAG
TACCAAGGCTGACACGTCATCTTTCCCAAGGACCATCTGCCTTCTCTCTT
TTCCCTCCTCTCCTGTGTAAAGGCCTGGAGGATGAGCACATGTGCTGTGTT
TTCCCTCCCTCTCAAAGCCTGTGCTATCTAATTAATCCCTTTTACCTCACA
GAAGGAGAACTGATGAAGCTGGCTGCCAAAAGGAATCAGCACGCCGGC
CCTTCATCTTTTATAGGGCTCAGGTGGGCTCCTGGAACATGCTGGAGTCG
GCGGCTCACCCCGGATGGTTCATCTGCACCTCCTGCAATTGTAATGAGCC
TGTTGGGGTGACAGATAAATTTGAGAACAGGAAACACATTGAATTTTCAT
TTCAACCAGTTTGCAAAGCTGAAATGAGCCCCAGTGAGGTCAGCGATTAG
GAACTGCCCCATTGAACGCCTTCCTCGCTAATTTGAACTAATTGTATAA
AAACACCAAACCTGCTCACTAACTTTCTGTCAATTGGGTTTCATTTCTCA
TTCATGCTTTAAGGATTTGTGTTTTTAGGATATAGCAAGAAGCTTGTTTA
ATTACAAAGTTCTGGGTTGGAAAGAGACCGGCTTCTGCTTGTGTACTGCT
ACCCTGAACCATCAGACATGCATGTGTGTGTGCATATGCTATGATGTGGCC
AGTCTGAGTGCAATACTTGCAGCGGGAAGGAGCAGCTGGGTGCATGCTGT
GCTCTAGAATTAGTCTTTCCTACTGGGGTTTGGTAGATTCTGAGGGCATT
GATCCTGGGGCAGAAGTGGCTGAGTCTGTGTCTAGGGTACAGTGTGCAAG
AAAGAAATGTAAACAGCAAGTCACAATCCAGCCAAGTGATAGTGGAAAAGG
GGTAGTTAGGTCCCAGATAAGGAGCAGGGTGACTTGACCTGTGGGAAAGG
CACAGAGACAAGGAATCTGGGTGAGATGACAGCCAGGAGACCAGGTGAGG
GAGGAGCCAGGTACTGTCTGGGAGGCTTGTCAACAAGGGCATGGTCCTAT
CACTAAGCAGGGCTCAGATCCTCATAATGGGGGAGTGGAAGGCTGGCCGA
ACAGAAATCAGGGCCTGGAAACAGAGTGAGGGGGTGGAGACAGGAGACTG
AGGCTTGGAAATTAGTTTATTAGTTTTAGCTCTTCAGTTACAAGCAATAA
TAATAGCTTCTAGCTTATTTAAGCAACAAGTATACTACAAAAGGAGCTTT
CTAGAAGGATATTGGGTATATTCAATTTCTTACTGCTGCTGTAACAAATTA
CCACCAACTTAGTGGTTTAAACAATGCAATGTATTATCTTGCAGTTATGG
AGGTGAGTCTGGAATGTGTCTCACTGGGCCAAAATCAAAGTATCAGCAGG
ATAGCATTGCTTTGGGAGGCTCTAGGGGAGAGTCAATTTCTTGCCTTTT
CCAGCTTCCAGAGGCCACCTGCATTCCTTGGCTAGTGGCCCACTCCCATC
TTCGCTGCTTGGGTTTTTCTCACACTGCTTTGCTCTGACCCTCCTGCCTT
CCTCTTTCACATATAAGAACGCTTGCAATTTACATCGGGCTCACGTCAAT
ATCCAGGATACTCTCCCGTCTCAAAGAGGCTTAACCTTTAATCACAGATGC
AAAGTCCCTTTTGCTATGTATGTACATATACACAGGGTCTGGGGATTA
GAATGTGGACATTTTTCGGGGTGCCATTATCTGCCTATCATGTGAAGTAA
CTTTCAAATGGAAAGACATGCTGAAGAAAAGTCAGGGATTTCTGGCAG
GCCAGAAATGACAGAAGGCAGAAAACGTTGGTCCCATCACTCAGATGGGT
AAGAGCCAATCATGCTTTTTGTGCTAGTCAAAAAGATTGAGATTCCAAGC
AAAGCATGCAACTGCCCTAGTTTGGGTGCTGTGTGCTGACTCCTTGGTCACT
GAAGGGCAGCACACCTTGATCAATACTCCCTCCAAGACTGTATCCAACGA
GGCCAGTGATGTTCTCAAAGCAGAGCTAGAGAGCTAATCCCAGGAGAGA
GGCGTGTGGGTGGTGGGCAGGAAGACAAAGCTCAGCCGTAAAGGAGTAGT
AGGGACAGCACCTAGGCATGGAGGCTCAAGTGAGATGATACCCATGGGA

FIG. 4 (55 f 61)

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AAAGCTCTGATAAGGTCAGCTCCTTCTGTTTCTGATCCTGATGGTGATGG
TGATCAACACCAGCCCAGTGACAAAAAGTACATAGTATATTTAGTAGAT
GTTTCCCACACAGAGAAATGGTAAATATTCAAGGCGAGGAATACTCCAAA
CATCCTACCTTGATCATTACACATTCCGTGCATGTAATGAGTACTTGCA
GTATGCCATAAATATGTGAAATATTATGTATCACTATATAAAAGAAAAAA
AAATGTGGCCAGGTGACATCCATATTTTGGAGAGGAAGGCATGTCTTCTT
CATAATATCACAAAACCTATTTTCACAACAAAGACACAGCTGTTCAAATTA
GTCTCTGAGCCGGGGCTGTCTCATGGCAGTGAGGACTCTGGTTCCCTTAC
AGACTAGCAGAAAGGAGATGGGGCTTACTGACCATGGCCTTGAGGAGGCT
GAACATGCAGGCCAAATGGAGACACAGACAGCCTGGGCTTGGTCCTGCTC
CATCCCCTTCCAACCTGATGAGATATAGTGAGTCACTATGACGTGGGTCA
CTCATGCTTCTGTGAGGCTCCACCAAGACAGCAAGTGCAACACCTT
ACGGAAGCACAAGGCCCTGTTTGTGTTGACTTCATGAAAGGCATGGTTG
TGGTGATCGCATTGAGTAGGCTTTTGGGTGAGAGGTGAAAAACCCCACT
ATCATGCATTGCAGCCCTCTGGTGGAACCTGTGCTTCAGGCTCTAAATTT
CAGGCTCTAGACTGACTCCAGGATGAGTATTTGGAAGCTGAAGTCAATCT
GTGGTCTCTTCTCCTGTAGAGCAGGAGTCAGCACTTTTCATAGAGTGCCA
GATTCTATATATCCTGCCACATGCTCTGTTGTTACAGAACAAGAGGCC
ATAGACAGCATGGCTGTGTTGGCAAATACACAAAACAGGCAATAAGCTGT
ATTTGGCCTTTAGGCTGCAGTTTGCCAACCCCTGCACTAACACAGAGCTT
AAAGGTGGTGGTGGTGTGCTGGAGCTAGCTTATATCAGCTTGCAATAGCC
AATTGCTAACATCTCTTCAAACCTCTGTGTCTGTGCCTTGATGTTGATAG
TTTGAAATTGGCTACCCCATTTAATGCTGCAATCTTTTCTCACCCCACT
CTACTGACTCCCCTTTGCCCTGTCTTATTTTCTCACTCTAACATGCTGT
ATAGTTTTCTTCTTACATTTATTGTTTGTGTCTTCCACTAGCATGTATGT
CCCACAAGTTCTTTGCTCTGTGATGTATCCCAAGAACCCACTGCAGTGCT
TGGCACTTGTAGGAACCTCATAAGATTTTATAAATGAAGAAAGGAAGAA
AAAAGAGAGGGAGGGAAAAAGGAAAGGAAGCCTTCTATTTAAATGATGGC
CTTCTCCATATTTCTATAGTAATATGACTTCCCTTGCAAAGGGGGATGCA
TTTTGGAAATGTGTATAAATAAACTCAGGTGGTTTTGAATTTCAATTTT
CTAACTGTAATTGTAATCATTGGTCTTTATGTTTAGTGAAAAAGTTTTGG
CCCTTATGCCTCACACCTGAGAATCCCAAAGTATTGGTTTGTTAGAGCTC
CCATAGAGAACCATAAACTGGGTGGCTTAAACAACAGAAATGTATCGTC
TCCTGGTTTCAGGAGGCCAAAGTCTGAACTCCAGGTGTTGGTTCATTCTGA
GAGCTCTGAGAGAGAATCTGTTCCAGGCTTCCCTTCAGTTTGTGGTAGCT
CCAGGGTTCCCTGGCTGGTGGCAGCAAACTCCAGTCTCTGCCCCCATCT
TCACATGACTGTCTTCTCTCTGTGTTTCTGTGTCCAGATTGTCCTATAAG
GACAGAGTCATACTGAATTAGGGCTCACTCGAATGACTTCATCTTAAGTT
GAACTGTATCTGTAAAGACCTTATTTCCAAGTAAGGTCACATTCACAGCT
ACTGGGGGATAGGACCTCAACATATCTTTTGGGGGACATAATTCAACTC
ATAATACCCAACATGATAACTGTTTCATCCCATGAAATTTAATGTCTCTCA
AAAGGTGATCTCAGGGCATTTAATCTGTGACAGAACTCCCATAGGAAAC
ATTCCAACCAGAAGCTCCTTTTCACAGCTGGTCACTCCTCCTACCCCATCC
GAGGTCTTGGGGCAGGGTGAGGCAGGTGGGGACAAGAAGAAGGCTGTCTC
GGGTGTAGAAAGAGAAGACCCTTATTCACCCGGCACTCTGTTTCATGAATG
AGCTATCCAGCATAGGATATAATAAATCGCTTTAGGAGTGGTAGACTCCA
AACATTTTTTTTGGTCCCAGTTATCCTAATCAATTAACAACTCTAGAAC
CCATCTTGAAGTGCAGGCATTGGGACATTATGAACTTACACAGAATTCA
AAAATTTACAAGGGCTAAATAAAACAGGGTCTGACATCTAATATTTTCTT
CCCACATTCCCATGCACTGTCTGGCTCAACCATCCCCAACCCCTCACTCTC
ATCCTGGTGGACACATGCCTAGTGATGTGATCAGCTGGTTCACAGGGGGC
TGGTGATGGTGGATATACAGCTTTTGCCAATTTCCATGGCATAACTACTC
CAAATATGGCCAATTTCAAACCTACCAACATGAAGGCACAGACACAGAGTT
TGGAAGAGATGTTAGCAATTGGCTATTGCAAGCTGATATAAGCTAGCTCC
AGCACAGCACCACCGCTACCTTTAAGCTCCTTGTGTTAGTGCAAGGGTTG
GCAAACCTGCAGCCTAAAGGCCAAATACAGCTTACTGCCTGTTTTGTGTAT
TTGCCAACACAGCCATGCTGTCTATGGCCTTCTTTGTTCTGTAAACAACAG
AGCATGTGGCAGGATATATAGAATCTGGCAGTCTTTAATAAGTGCTGACT
CCTGCTCTACAGGAGAACACAGATTGTCTTCAGCTTCCAACATTCTATCT
CTGAGTCAGTCTAGAGCCTGAAATTTAGACTGAAGCACAGTTTCCACCAG

FIG. 4 (56 f 61)

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AGGGCTGCAATGCATGAAGTTGGGGTTTTACCTCTCACCCAAAAGCCT
ACTCAATTTTTTTACTGCAAAAACATGTTATCATCATTATTTTTTTACTTAG
CCCACCTTTTCCTTGGCAATTTTCCATAGGAAAATGCATTCTAAATTTCAA
CTAATCAGGGGACTTGGAGCCTCTGGACACCCCCCTTGTTCCTTGCCCACA
GTCCCTTGCGAAGGTGCCTTATCAGAGCGGCTCCATGCAGGGGCTCAGG
ACAGGATCAGATGTCAGTTGCACCAAGGGGGCAGGGACAGATCCTCTCTG
CTEACCATGCAGAAGGGACTGTTCACTGCACCGTCATGGTCCTGGTGATT
TCTGGTCCATAAGGGGAATTTTCACATGCATCGGGTGATTGTCACATCAGC
ACAACACTGTGAGGAAGGCAGAGTGAGAATTTGTGTGCCCATTTTTATAGG
TGAGAAAACAGATGCAGAGACATTAAGTAACTTCACCACAGTCATGCGGG
TTTTAAGTGGCAGACTTTCAGGTGTTGTGACTCCTAGTCCAGAGTTCTTT
GCACTGCCCCCTGAGGTGCTAAACTCTACTGTGCTTTAAGACTCACTTGG
GGAGCTTCCTAAAAAGAGAGATTGCACAACCTGAGATTCTTGTTTAACTG
TTTTGGGATGTAGCTCAGGGATCTAGCTGCCTTAAAAAAAACCTCCCA
AGTAATTCTGATGCAAGCGGTTCTTTTTTGTCCACCTTTGAAGAAACACT
GCCTCCTCCCCATACATTTTATTAGAAAATGGTAACATGTTTTTTCAGCCT
GAGAGCCATTTCTGGGTGACCGGACGTCGGCAGCCCGCTGTACTAGCTTT
CAGTCTAGGCTTAAACACACATGATAGGAGATGTCCTACTCCAGATGATA
TGAGTCTGAACCATGGAAAAATTCATTGTGTGGCACATCTGGTGGGTGT
GCACTGTCCCCAGCAGTGAGGCACCCAGTGAAGACAGCAGCTGGGAGAGG
CTTAGTTACATGCAGTGGGACAGTGTGGGCTAGACTGCTGAGCCCTCTGC
AGTTTACTCTGTGTGTCAGGCAATGAGGGTGAAAGGCTGATCAGACCCACGT
GCAGACCATAACCTCCAGGGAGACAGATATCAGTCAGGACAACCCCAAGT
GTAGCTGGAGAAGCAGTGCCCAAGGTATGACCGGATGTGTATCCAACCAGG
AAATCTGCATATAAATATAAGAGGAGAAAATGAACAGATGTTGCTCTTAT
ATGTAGATATTTATGAAGAGCATATAATTTTGTGTTTGTGTGTTTAAAGAA
GTTTATAAGTATGCCTTAAAAATGTATAGTATATACTGTAGGTATTTTTT
CCATTAGATATTTTGTGTTTTTCATACTTATCCACATTGACATTGTAGCAAC
AGTATAATATAACAACCTCCTCTACAAAAGCAGAAGGAAGTGAAGCTTTG
GAAGGAAGCACCCAGTGAGCTTGCCCCCTTTCAGGTGGGTGCAGTGAGCAG
GAGTCAGTGAGGTTGAGATCCTTTGAGAGGAGGCAATCATTAAACCAGGAA
ATCTGCACTGCATCCTGGCCACACCTAACCTTGGACAATGGTGCTTGGA
GCGCCTTCCAGCTCTTAAGGCTTGCGATTTCTTTCTCTCACTCTTCACCC
ACGATGATTAAATCTTCTCCTACAGAGTTGGACAATAAAGCCTTGAGTTC
CTGCCTCCCCCTGGTGTGATCACGAGGCATAGACATGGCCAGGAACATGTA
GGTGTCTTTGAAAGCTGAACAAGTTAGTAAATTTCAAACCTCATTTCACC
CACCAGTAAAATGGGAATAATAATAAACCTATTTTACATAGGGTTGACAA
GAGGAGTAAAGAGGGATTCAATGAAAGTTCGTTATTATCATTGTAGTAG
CAGTGTTGATAATATCAACTGAAAGTTCATTATCATTATTAGTAGCAGTA
TTGATAACCTCTTTTCTGTGCCTTCTCACTGGTGGGCCCAGGCCATCAG
CAATGCCCAGGGTGTGATGATCTCTGCTGCATCGGGCACCAGCTGTGTC
AATGGTGAGAACAGTACAAGGGTGGGCAGGGCAAGGCAGGAAGCACCCAG
GAGCAGCAGCTTCATGGGGTGAAGATGTCAGGAGCTTAGGGACAGTCAGA
GCGGGTGTGCCTCCTCTTGTTGGAGCCTTTCTGCGTGGGTAGGAACTGCTG
CAGCTGTGGCCATGGATTCACCTGAATATGGGTGGAATTAGGCATTTCAGC
TGGGTTAGCTGTGCCTAGAAGGAGGAACCTCTAAACTGAGAACTTGTCCTT
ATTGCCACCTCTGATAGGCAGATGATCCATCCATCAGTGGCTGAGCTGAG
GTGTGCATGGGGATGGGTAAGAGCCACACACAGGGCTGATGACTGAGTC
TATTTAGAACAAATAGATGTAAATCTGATAATGTAAATGTGATAGATTA
TTTTGTCAATTAGAAATGGTACCATATAATTATATATATACATAAACATG
TATACATATACACACATATACATGTGTGTATAAACACACACAGTATTGTC
CCCTACTCATTCCATAAACCTGATGCCTTTAGCTGGGATTCCCAGCTTTC
ACTCTCCTCTCTGTCATCTGCTGTCTATATCCTCCCCATCCTGTAATTCT
GGCTTATATGCCACTTCCTCCCTAAAGCCCTCCCTCAATCCCTTGCTGGA
AGTGACATTTTCTCTTTGAGCTGCCCCCTGCTTGTGCTTTGGTGAGGTCA
GCTGTATTGCAGTACCTTGTATTGTGGTTGTACATCATCGTATAGAATT
AATTTCTGACACATTCCGTATTTTTCAAAGGGCCTAGTGTGGGGCTTTAA
CAGTAACTACGCCACCACGCCAGTTAATTTTTTGTATTTTTTGGTGGAGA
CAAGGTTTCACCATGTTGGCCGGGCTGGTTTCGAACTCCTGACTTCAGGT
GATCTGTCTGCCTCAGCCTCCTGGAGTGCTAGGATTGCAGGCATGAGCCA

FIG. 4 (57 of 61)

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CTGCACCCAGCCACCTATCAAAATTTTAAGTGCCATTTTATTATTTTATT
TTTTGTAGAAATGGACAAGCTGATCGCAAATTCACATGGAATTGCAGGA
GGTTCCAAATAGCCAAAACAATCTTGAAAAAGAAGAACAAAGTTGGAGGA
TTTACACTTTCCAGTTTCAAGACTTAGCTCTTAGCTACAAAGCTACAGTA
ATCAGAACACTATGGTCCTGGCATAAGTGATGCTGGACAGGTGAGCCCCA
AAGTGGGACTTAACCTGTGAAGGTTCTTGGCCTTGCCCAGGAAGGAATTC
AAGGGCAAGCCAATGGGACAAGAAAACAGCTTTATTGAAGGGGCAGTATT
ACAGCTCCAGCCCTGTTACAGCTCCAGCCCTGTTACAACCTCTGACTACTC
CTGCACAGAAGGGCTACCCTGTAGGCAGAGAGTAGCAACTCAGGGCAGTT
TTGCAGTCATTTATATCCACTTTTAAACACATGCAGATTAAGGGACAATTT
ATGCAGAAATTTCTACGGAATTGGTAATAACTTTTGGGTGATGGAGTCAT
CATGGAAGGGGGGCGGGGAACCTCCCTGGTGTGTCATGATGACGGTAAAC
TGATATGGCGAACTGGTGGGTATGTACATGAAAAGCTCCTTCCACCCCA
GCCCTGTTTCAATTAGTCCTCGGTTTGGTCCAGTGTCCAAGTCCTGCCTC
CAGAGTCAAGTCCCACCCCTACCTCTTAAGGAGAGATGTAAATACATGG
AATAGAATTGAGAGTCCAGAAATAATCTCATACTATGATCAATTGAT
TTTCAGCAAAGGTGCCAAGACCATTCAATGAGGGAAAGAATCATATTTTT
TTCAACAAATGGTGCTGGATAACCATGTGAAAGAATGCAACTGGGCCC
TTATCTCACACCATATACAGAAATTAACCTCAAATGGCTCAAACACTTAC
ATGTAAGAGCTAAACTATAATATTCTTAGAAGAAAACAGGGATATATCT
TTATGACCTTGGATTTGCTGGCTGATTCTTAAATGACACTGAAAGCACA
GCAACAAAAGAAAAAAAATAGGTAAATTGGACCTCATCAAATTTAAAA
CTTTTATGCTGGGTGCACACCTGTAATCCAGCACTTTGGGAGGCTGAGG
CAGGAGGATCTCTTGAGCCCAAGAAGCTGAGGCTACAGTGAGCCGAAAT
GTGCCACTGCACTCCAGCCTGGGTGACAGAGCAAGACCCTGTCTCGAATA
AATAAATAAACAAATATATAATTATAGATCTCTGGATCTTGCCTTCGGAG
ACTGACTCAACTAACTGGTCTGGGTGGGAGCCAGCCATTTGTATTTTT
GAAACTCTCCAAATGATTTTACTGTGCAGCCAAGGTTGAGAATCACTGT
ATCATAGGGTTGGACTCCTAACTGGAAACAGTTTGCACCATCAGGTGTG
CAGCATTCTGATAATAGTTAAGCTTTCCTCCTAGATTTTCTGATATTAGA
TGAGTCATGTTTACAAGTTTTTACCAAGAGACAACTATCTTTCTGCCCT
TACTTTCTCTCTTATACTATTCTAATCCCAGAACCTTTGGAACTTCCAC
TGAGAGATGAATCTAGAAAGTGACTCTCTTGGCTACAACAGAGAGTAATG
TTGGCCTGTTTGTGCCAGATCCAGTTGGTGTGCTGGTGGTGGGACAGCACCT
CCCTGAAATCCCCTCCTCTCCCGTCAGATTCAGTCCCCCATTTGCATCAC
GTACAATCATCACTATGGGTTTCTATTACCTTGCTAGGGCATTGAGGT
ACCATATATACCAACTATTAGTTTTTGAGCCATGGTTCCCAAAGTGTGGAC
TGTAGGGCACCTCAGCACACTCACGAGGTGTCATGGGATATTTAAATATT
CTGAAGAAAACACAGTGACATCTGTGAGGCCCGTGAAAACCGTTGGCATT
AAATTGTCTCAACCCAATTGCTTAAGAAGCAGAACTGGCCAGGCACGGTG
GCTCACATCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGCAGATCAC
GAGGTCAGGAGTTCGAGACCAGCCTGACCAACATAGTGAAACCCCGTCTC
TACTAAAAATATAAAAATTAGCCATGCATGGTGGCATGCACCTGTAACCC
CAGCTACTCAGGAGGCTGAGGCAGGAGAATTGCTTGAACCTGGGAAGCGG
AGGTTGTAGTGAGCCAAAATCGTGCCACTGCACTCCAGCTTGGGTGATAG
TGAGACTACATCTCAAAAAAAAAAAATGAGAGAGAGAGAGAGAAGCAGA
ACCATCAGGTGTTTCTTTTGGCTTAAAGTACTCTGTGAAGAAATTCCTGG
GACACGAAGGATACCATGAACTGAGAGATTTTGGGAACCTCTGCTTTAGA
AGCTGGAGGTAGCATTCTTGGGCACAGTACTGCCTTGGGATCAGCAAAT
CCTTTTGTGCTTGGAGACAGAGGGAAGTATTGAGCTGCCCCGATAAAGAC
ATGCCAGCCTGGCAGAGTGTAGTGACTCATGTCTGTAATCCTAGTGCTTT
GGGAGGCTGAAGTGGGAGGATTGCTTGAAGGCCAGGGGTTTGAGATCAGCC
TGGGAAACAACAAGACCTCTACAAAAAAAAAAGAAAAAAAAAATTAACCA
CATGTGGTGGCATGCACCTGTAGTCCCAGCTACCTGGCAGGCTGAGGTAG
GAGGATCACTTGAGCCCAGGAAGGTAAGGATACATTGAGCCATGACTGTG
CCACTGCACTCTAGCCTGGGTGACAGAAAGAGACTCTGTCTCAGAAATAA
ATTAAATAAATAAATAAATATATAGTGCCATGACATCCCTAGAAAGACA
AGGTCCTGGGAATAGGTAGAAGCCAAGGGAAATGAGAAATGAGAGGGGGC
CCTGGAGCTGGAAGTGGGGGAGCAGGATGGCCTCTGAGAAGTTCCTGATA

FIG. 4 (58 of 61)

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GTGGTGTCACTGATGTGTCTGATGTTTAGTTGTAATTATTTGCTGGGCCC
CTGTCATCCCTCATATCTGATAGCTCTTTGCTAGTCAAAGTGTGGTCTGG
GGATCAGCGGCATCAGCATCACTTGAGAACTTGTTAGAGATGCAGAATCT
AGAGCCCCACCCGGGACCCAGAAACAGAGCCTGCATTTTAACAAGCTCCC
CAGGTGATTCTCACACACACTCGCATTGAGAACTGGGCTAGTTGAC
AGATTCTCAGGCATGGCTGACATTGAAATATCCAGGGAGCAGGCTTGGCA
TTAGGATGTTTAAAAGTCCTCCAGGTGTTTCTAAAGCCAGGTTTGAGGAA
TTACTGGGCTGATACAAATGTTTTGTGATGATGCTTTGTGTGTGTGTGTG
TG
TGGGTCACTTGGCACCAACACAGGAAACAATGGAAATATGTGAGCCATGA
CAGAAAGGTCAGGAGATAAAAGAAATTAGTGACATGAGAGGTAATCCTCA
GGTGTAGGAAAGAGGGTAGAGCAAACAGGTTTTCCACCATATGTTGGA
TAGGGGGTCAAGTAAATTTCTACTTAAAAATTACAAACAGGGGCTGGGCG
CGGTGGCTCATGCCTGTAATCCCGCACTTTGGGAGGCTGAGGAGGGCGGA
TCACAAGGTCAAGAGATTGAGACCATCCTGGCCAACACGGTGAAACCGTG
TCTCCACTAAAAATACAAAAATTAGCTGGGCATGGTGGTGCCTGCTTTA
TTCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCTGGGAG
GTGGAGGTTGCAGTGGGCCGAGATCGCACCCTGCAATCCAGAGCGAGAC
TGTGTCAAAAAAAAAAAAAAAAAAGAAATTCCAAACAGGATGACCCTAAG
CCTGCAGGACTTGGAGACATCTAGGTGACTGATACTCAGTCACAAAACAT
AATTGGTCACAGGCCTGATGAAATGCACAGCAGACCTTCAGATGGTATGC
ACTCAAGTGATATCCACAAGTCCACCTAAAGAAATGCTATATTCAGACAT
TTGGCATCAATCTCTATCAAACAAAGATAGTCCAAAGCAATGGGTCCAA
AAACACTTTCCTAAGACAAATTCTCTATTTGCTTTTAATATCAGTCATCC
CAGCCCTTGAATAGAGGAGCAAATGATACCAGTGGTACCCTACCACAAT
GCACCAAGGTATTATACTCTCATGCTCCATTTCTCCCTCTGTCTACATC
ACTAATAACTCATTGATTTCTGGTGCAAGCCCTGCTGGGAGAAAAAGTCT
ACTCTTGTAACCTTGGAGCAAGTTGCTCAGAGTAGGTATCGAGGATAAAAT
TTGGAAAGTTAGAAAAGCTATTAGAAGGAGATCCTAGTAGTTGAAAACAC
AGCCTGGCCAAGTCAATGATGCTATTTTCATCTCCCAGCCTTGCTATGTC
ATAGCTAAGGAAGACAATTTAGGCTTGGGCTAGAGGATGGGAAAGGGCAA
AATTACTGATGCCACAGCCCAGAGAGGTATTCTAGTAATCTGAGGGTGAG
GACCACATACCTGGTTCAGGGACGTACAGTGTGACAGCTGTGAGTGGAT
GCCTGGAGTTCTGGCGTGTCTTCTAGCACAATGATACCTGAGACTCTTGC
ATCATTGGGAATAATAAAATGGGAGTGGATAGATATGAAATTATGATGGC
AATAAGCAATCAGCTAATAGCTTCATTGATGGGACAGATTAAAGATGGCT
GCAAATCCTTTGGTCCAGGTTTGGGATATAGGCAGCATTTGTATTGGAAT
GCTGATAGTCTGAGGCCATGAAAAGTCCACCTGCAGTAGTGGTAGGAGGA
ACAAGCCTCACTTTCTTCAATGTGTGTGACTGCTGTCTTGATTCCCTGGG
TGGCCAGTTCCATTCTGTGTGGTTCTTTGGTCCACTTGACTCTGGGGTGGC
TCTGTGATGGCTTGACCAATACAATGTAGTGGAAATGATGCTGTCTCATCAT
TTCCAGCCTCTTCCAGCCTTAAGGAACTGGCAACTTTTATTTCTGTCCCT
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CCCTAGCTGTGCTCCTAGCTGACAAACAGTAGCAACTTGTCACCAGGCGA
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AAATAATCCCCTAGGCTTTGGGCTGATTTGTTCCAGATTACTGGAACAGA
ATTTGGTACCAGGGGTGAGGTGCTACAGCAATGAAAGCTTAAGACACGTG
ACTTTGGTTTTGGGTCTGAGTGGCAGGGGAACTTGGCAGGCCTCAAGGAA
ACTTTTAGGGAGGGTTGAAGCATAGTGAGGAAACAGTAGGGGAAGCTAG
AGGAAAAAATGATGCTTGGTATGTAGTGGTGGGAAGTTTAGCAAACTCG
CCTGATGTAATGTGGGAAATTGTAAGAACTCAGAACGATTTAAGGGCATG
TTTTATAGGTCCTTTAAGAACTTCTAGGCCAGGCGCAGTGGCTCATGTC
TGTAATCCCAGCACTTTGGGAGGCTGAGGTGGGCGGATCACAAGGTCAGG
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ACTAGGGAGGCTGAGGCAGAAGAATGGCGTGAACCTGGGATGTGGATCTT
GAAGTGAGCCCAGATTGTGCCACTGCACTCCAGCCTGGGCAACAGAGTGA
GACTCCGTCTCAAACCGAAAAAAGAAACTTCTAGGGC

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TGGTCCCGTGGAAGCCTCACACATGGTACACAAAGGCTGTCTTGAAAAGA
AACGTAAGTGTGTTTTTTGGTTTAATAAAATTGATTATAAATGGATAATG
CAAAACATTTTAAAGAATTTTACTAGCTTACATTAGCAGATTTGGATCCA
GTGATTGTTACATTCTGGTACTGAGCCCCCTGAATTACTTCTTTGAGTAAG
GCATTATACCAAAGCTATTGATAGTTGGGCTTATAGGGTGTATGTTTGAA
GAACTACTAATGTCAAACCAATATTTACCGGTCGACAAGAGGACATCAG
AACTGGTAATCCTTATTACCATGACTGGCTGGACAGAATACTCAATGTAA
TGGGATTTCTTGCAAATAAAGACGGGGAAGATGTAAAAAAGATGCCTGAA
CATTCAACATTAATGAAAGATTTTCAAGAAGAAATATGTATACTAACTGCAG
CCTTATCAAGTATATGGAAAAACACAAAGTTAAACCAGATAGTAAAGCAT
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TTTCAACAGTTGTCAAATCCCCTACCCAAAATGAGAATTTTAAACAGAAG
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CATAACCACACGAATGGAAGTGGCCACCCAGGAATCAAGACAACGGTCAC
ACACAGGGGACCCCCGTTGAAGAAAGTGAGGCTTGTTCCCTCCTACCACTAC
CTCAGGTGGACTTTTCACGGCCTCAGACTATCCGCGTTCCAATCCACATG
CTGCCTATATCCCAACCCTGGACCAAGCACATCCCAGCCGAAGAGCAGTG
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TGCAGGGCTGACTGTGCAGCTCTCCGTGGGAACCTGGTATGGGCGCATGAG
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ACCTGAAAAGAAAGCGCTAGCACAGTTTGTGTTGTGGATTTGCTACTTTC
ATAGTTAACTTGACCTGGCTCAGACTGACCAGTACTTTTTTTTCCGTGAC
AGTCTATAGCAGTTGAAGCTGAGAATGTGCTAGGGGCAAGCGTTTGTCTT
CATATGTCATGAATTCCTCCAGTGTAACAACATTATCTGACCAATAGTAC
ACACACAGACACAAGGTTTAACTGGTACTTGAAAACATACAGTAGGTGTT
AACTCAGTGAAATAACCAGGACTCAAAGTAAGATTATTTTGGTACACCTT
TCTTGTTAGTGTCTTATCAGTGAGTTGATTCATTTTCTACATTAATCAGT
GTTTTCTGACCAAGAATATTGCTTGGATTTTCTGAAAGTACAAAAAGCC
ACATAGTTTTTTTCAGAAAGGTTTCAAACCTCCTAAAGATTAATTTCCAA
GTATAAGTTTGTTTTTTATTTTCAATCTATGACTTGACTGGTATTAAAGCT
GCTATTTGATAGTAATTAGATATATTCTCATTGATATAAACCTGTTTGGT
TCAGCAAACAACTAAAATGATTGTCACAGACAATGCTTTATTTTTCCTG
TTGGTGTTGCTTGTGGGAAAAAGAAAGAGAGATCAGATTGTTACTGTGTC
TGTGTAGAAAGAAGTAGACATAGGAGACTCCATTTTGTCTGTACTAAGA
AAAATTCTTCTGCCTTGAGATGCTGTTAATCTATATAACCTTACCCCCAA
CCCTGTGCTCTCTGAAACATGTGCTGTGTCCACTCAGGGTTAAATGGATT
AAGGGCGGTGCAAGATGTGCTTTGTAAACAGATGCTTGAAGGCAGCATG
CTCGTAAGAGTCATCACCCTCCCTAATCTCAAGTACCCAGGGACACAAA
CACTGCTGAAGGCCGACGGGACCTCTGCCTAGGAAAGCCAGGTATTGTCC
AAGGTTTCTCCCCATGTGATAGTCTGAAATATGGCCTCGTGGGAGGGGAA
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GGATTAGTATACGAGGAAGGAACGCCTCTTTCAGTTGAGACAAGAGGAA
GGCATCTGTCTTCTGCCCCGTCCCTGGGCAATGGAATGTCTCGGTATAAAA
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TATGTGTATGCATATCTAAAGCACAGCACTTAATTCTTTACCTTGTCTAT
GTTGCAGAGACCTTTGTTACAGTGTTTATCTGCTGACCTTCTCTCCACTA
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ATCAATAAATACTAAGGGAACTCAGAGGCCGGCGGGATCCTCCATATACT
GAACGCTTGTCCCCTGGGCCCCCTTATTTCTTTCTCTATACTTGGTCTCT
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CAGGTGTAAAGGGGCAACCCACCCCTTCATTGCTGATTTGTGAGCGTGCT
TTAAGGTGAAAAAAGCATGAATGTTAACTTCTTAAAGGTACAGCATC
CAATTCAAATATTTTTGTCTGATTTTAAATGCTAGTTGATGTAGTGCTAT
TAAATTTTGTTCACATGGACACAGAGAGGGGAACAACACATACCAGGG
CCTGTTGCGGGGTGGGGATGAGGGGAGGGAACTTAGAGGACAGGTGAACA
GGTGCAGCAGATCACCATGGCCACATATACCTATTTAACAACCTGCAC

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GTTCTGCACACGTATCCCATTTCTTTTTTTTTTTAAGAAATAGAAAAAA
AATAAAATTTTGTTCACTGATTCTTCCATTTTAAACTTGTTTGCATGTG
GTTTAGGATGCCCTTACTTCAGCAAAGGAGAAGGAATAGGAGGGCCTTAG
AATTTTGTAGGGAAAAAAACCTATAACATACATTGTACTGTATCAAAC
ATTTTACATGAATGACACAAGTATTCTGAATAAAAAAATAATTGAACATT
GTTAAGAACAAGGTGTCATGTAATTTATTTTTCATAAATAAAAAAATTAT
AGTGGCTTAGACTGAAAGGAACAGAGAATTTAAAAAATTAAAAAGAAGCC
TTAGTATATTTTTGTATATAGTTTCCATGTGCCATATTTGCCATAATTGG
ATGAGAATTTTTTGACCTCTGGCAGGGTGACCCTATATTTTCANTNTATA
AAGCGTGCATCATAACC

MVLKCHPPGDSQCAPGVRVTALGHATQRVSSDQQIIPQI.WECIRKTEAWIHPIL.I.NIISI.QPGGPCSI.SNKC.I.SSI.QRSASA
 EKGSPILI.GVSKGEFCI.YCDKDKGQSIPSL.QI.KEKI.MKI.AAQKESARRPFIFYRAQVGSWNMILESAIIPGWFICTSCNCN
 I:PVGIXNXVIDFDI.I.GKAQKRGTGSE

FIG. 5

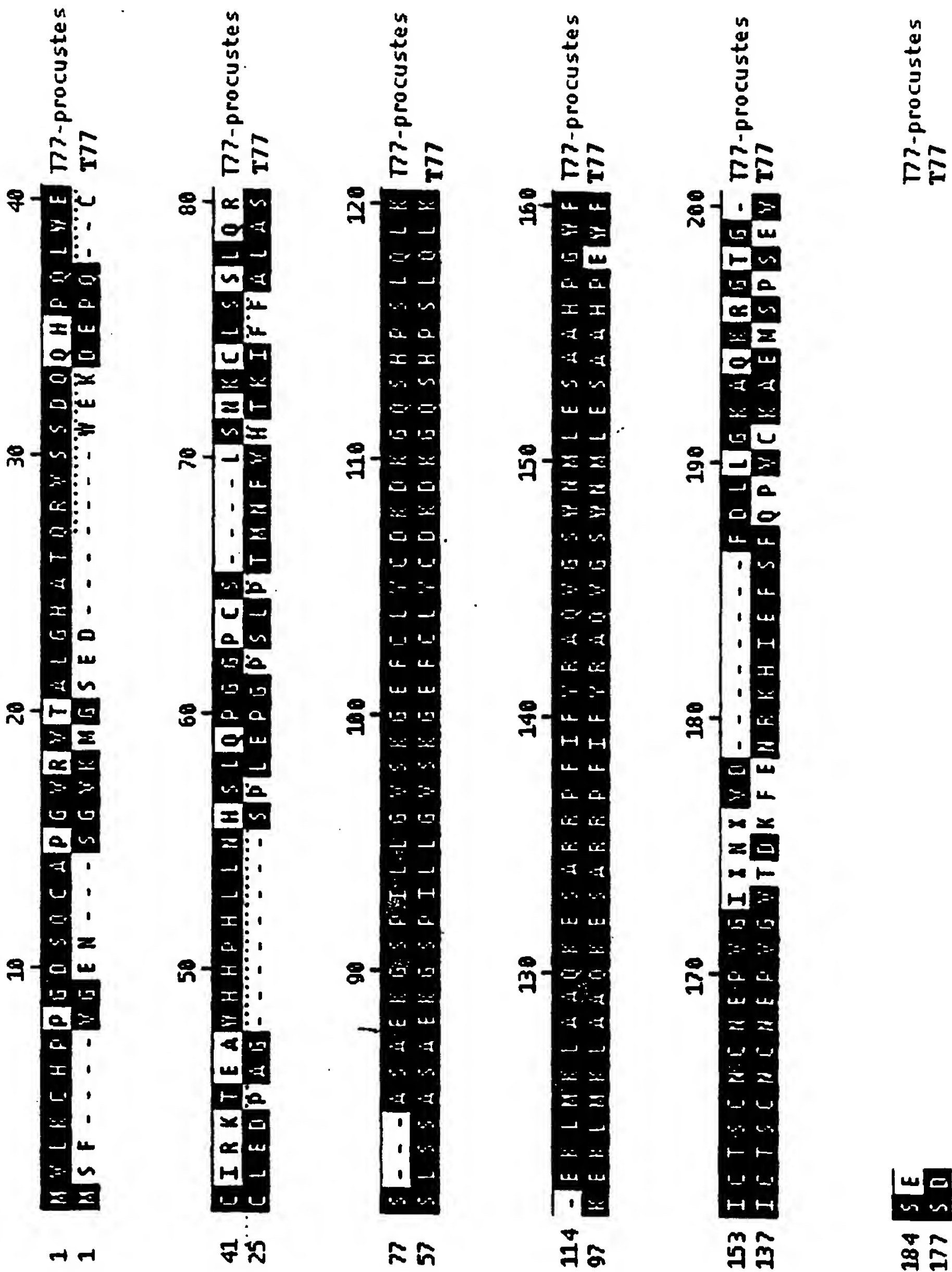


FIG. 6

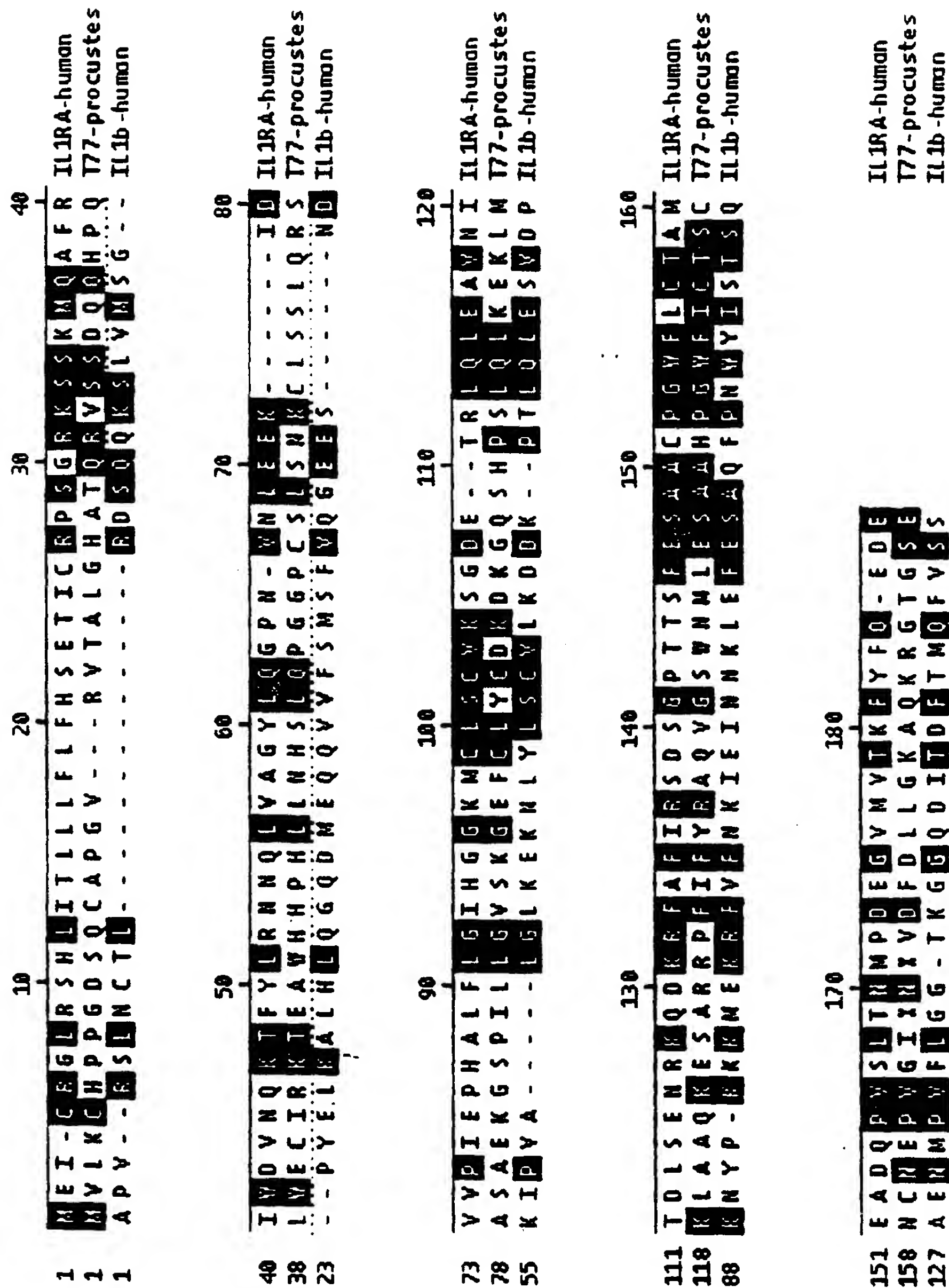


FIG. 7

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/16102

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07H 21/02, 21/04, 1/00, 14/00, 17/00; C12Q 1/68; G01N 33/53

US CL : 536/23.1; 530/350, 387.1; 435/6, 7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1; 530/350, 387.1; 435/6, 7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG: MEDLINE, USPATFUL, WPI, BIOSIS. Search terms include author, "TANGO" and protein

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database Medline on Dialog, US National Library of Medicine, (Bethesda, MD, USA) AN 09370320. SONNENFELD et al. 'The Drosophila tango gene encodes a bHLH-PAS protein that is orthologous to mammalian Arnt and controls CNS midline and tracheal development'. Development. November 1997, volume 124, number 22, pages 4571-82, Abstract.	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 OCTOBER 1998

Date of mailing of the international search report

30 OCT 1998

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